

*Photoinduced Electron-Transfer
and It's Application to Natural
Product Synthesis*

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Outline

- **The Basics**
- Formation of Iminium Ions
- Reactions Involving Iminium Ions
- Carbonyl Reductions Using Amines
- Arene Acceptor Reactions
- Cyclizations

All You Ever Wanted to Know About Photochemistry

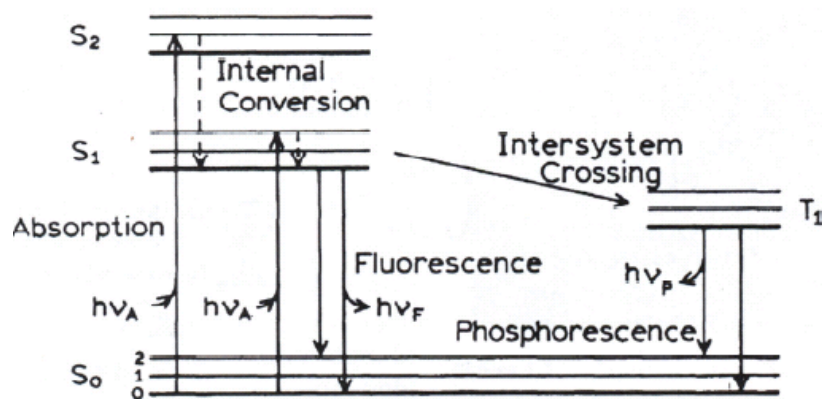
The Basics

Photochemical Processes: the interaction of light with matter leads to any of large array of chemical structural changes

Ground Electronic State: all electrons are in the lowest energy molecular orbitals

Excited Electronic State: brought about by the absorption of a photon of UV/vis light and usually involves the promotion of an electron in a bonding orbital to an antibonding orbital

The Jablonski Diagram



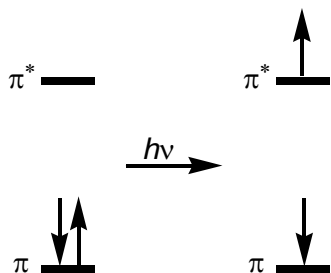
Kasha's Rule (guideline): All photochemistry is initiated from the lowest excited states S_1 and T_1

- S_0 to S_1 transition is instantaneous (10^{-16} to 10^{-14} s)

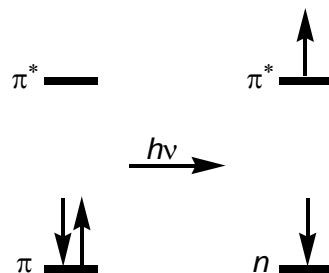
- Nuclear motions are slower (10^{-13} to 10^{-12})

π, π^* and n, π^* Transitions

Electron Transitions



π, π^* transition



n, π^* transition

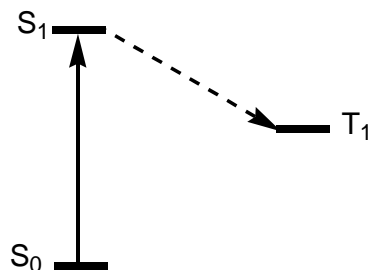
Chromophores

- A functional group that absorbs UV/vis light

Chromophore	Type
Benzene	π, π^*
Styrene	π, π^*
Acetophenone	n, π^*
Naphthalene	π, π^*
Anthracene	π, π^*
Nitrobenzene	n, π^*
C=O	n, π^*
N=N	n, π^*
C=C-C=O	n, π^*, π, π^*

Intersystem Crossing

Electron Transfer Initiated Cyclizations

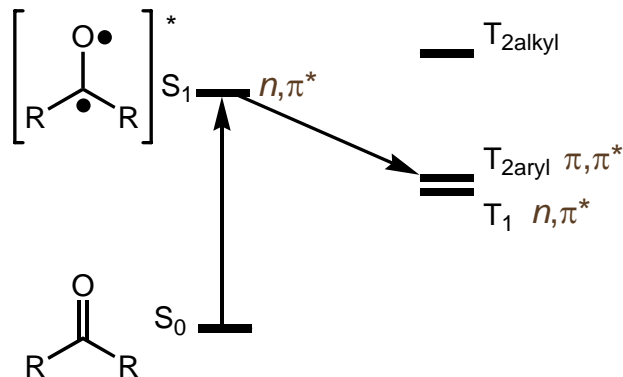


- The S_1/T_1 gap is smaller for n,π^* states than for π,π^* states

EI-Sayed's Rules

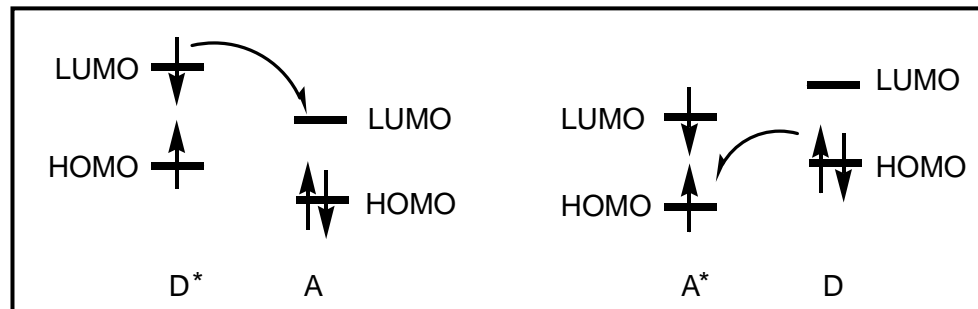
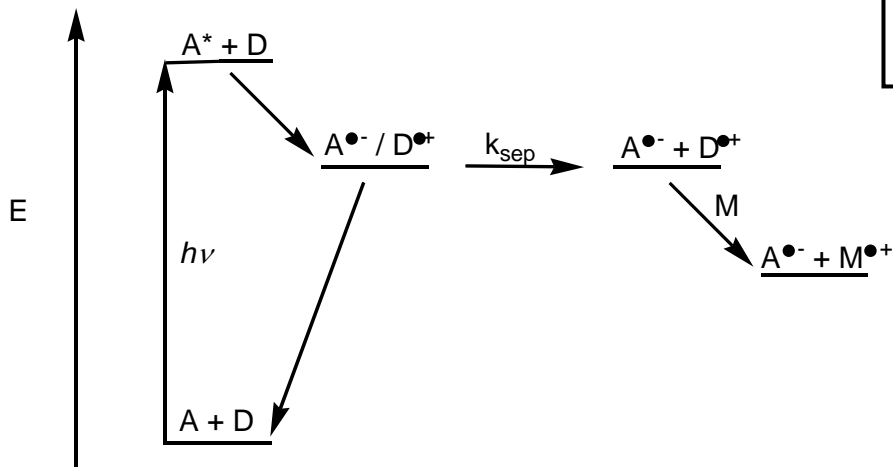
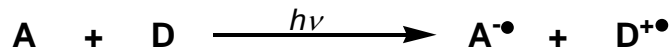
- ISC is slow when the two states being interconverted are both π,π^* states or n,π^* states

so...

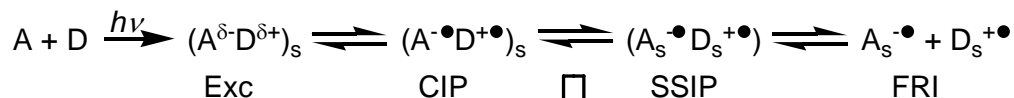


Background

Photoinduced Electron Transfer



Things to Consider



↓
Salt Effects
Solvent Polarity

Gould, I.; Ege, D.; Moser, J.; Farid, S. *J. Am. Chem. Soc.* **1990**, *112*, 4290.

Mattay, J. *Synthesis* **1989**, 233.

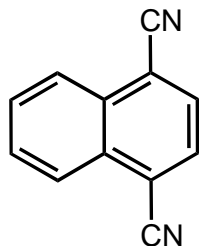
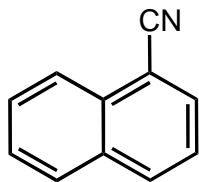
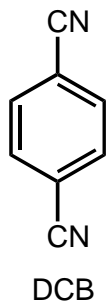
Mattay, J. *Angew. Chem. Int. Ed.* **1987**, *26*, 825.

Electron Transfer Sensitization

Requirements for Photosensitized Reactions

- Light is not absorbed by the substrate that undergoes the chemical reaction but by the sensitizer
- The sensitizer must not undergo any sort of chemical change (i.e. it must undergo a reversible redox process)
- The sensitizer must completely absorb the light in order to avoid competing reactions
- It is necessary that the sensitizer be able to be removed completely from the reaction mixture

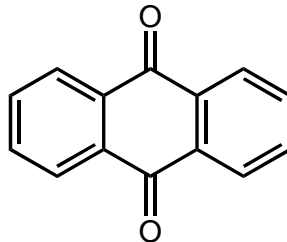
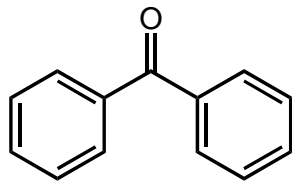
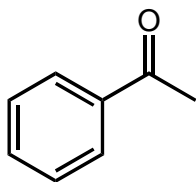
Typical Electron Transfer Sensitizers



Common Features

- Aromatic molecules
- Absorb in the U. V. or even in the visible region
- The singlet or triplet energy of the sensitizer is greater than the singlet or triplet energy of the acceptor

The singlet excited states undergo redox chemistry



Energy Transfer



The triplet excited states undergo redox chemistry

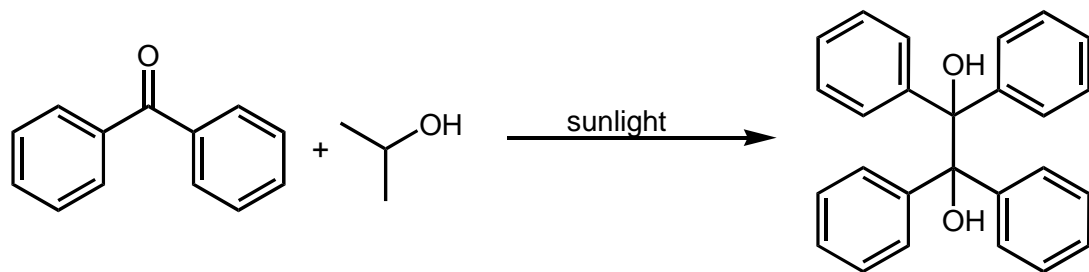
Early Photochemical Reactions

Some Thoughts on Sunlight

Photochemical Syntheses utilizing sunlight are not in general, and especially on an industrial scale, suitable for use in Europe or in the northern part of America, where sunlight is unreliable and often unavailable; this is also the case in many other parts of the world. In tropical and many subtropical regions, however, conditions are different, so that the prospects for the industrial development of such synthesis can be considered promising.

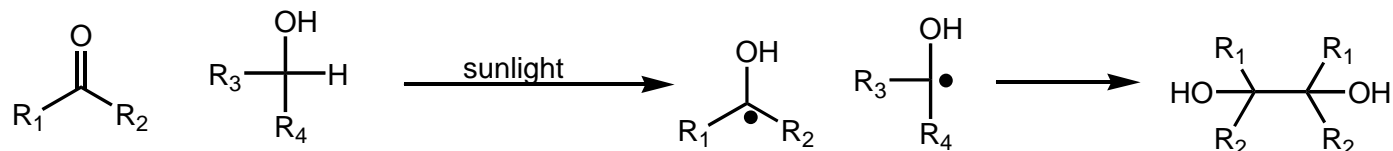
Schonberg, A; Mustafa, A. *Chem Rev.* **1947**, *40*, 181.

Photochemical Pinacolization of Non-Enolizable Ketones

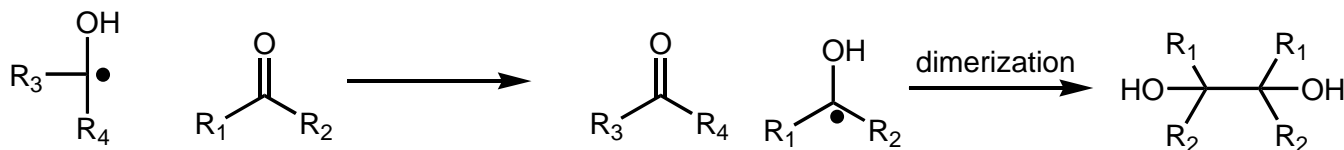
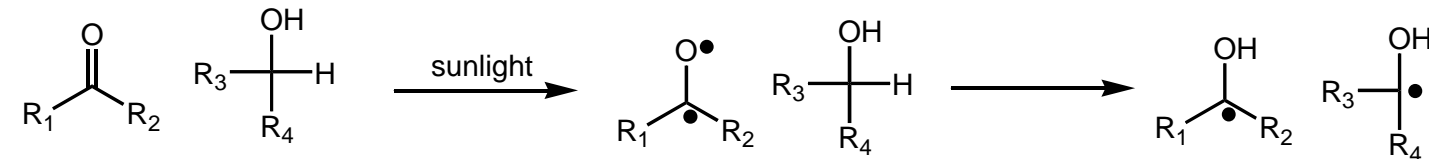


Schonberg, A; Mustafa, A. *Chem Rev.* **1947**, *40*, 181.

Proposed Mechanisms



Weizmann, C.; Bergmann, E.; Hirschberg. *J. Am. Chem. Soc.* **1938**, *60*, 1530.



Pitts, J. *J. Am. Chem. Soc.* **1958**, *81*, 1068.

Outline

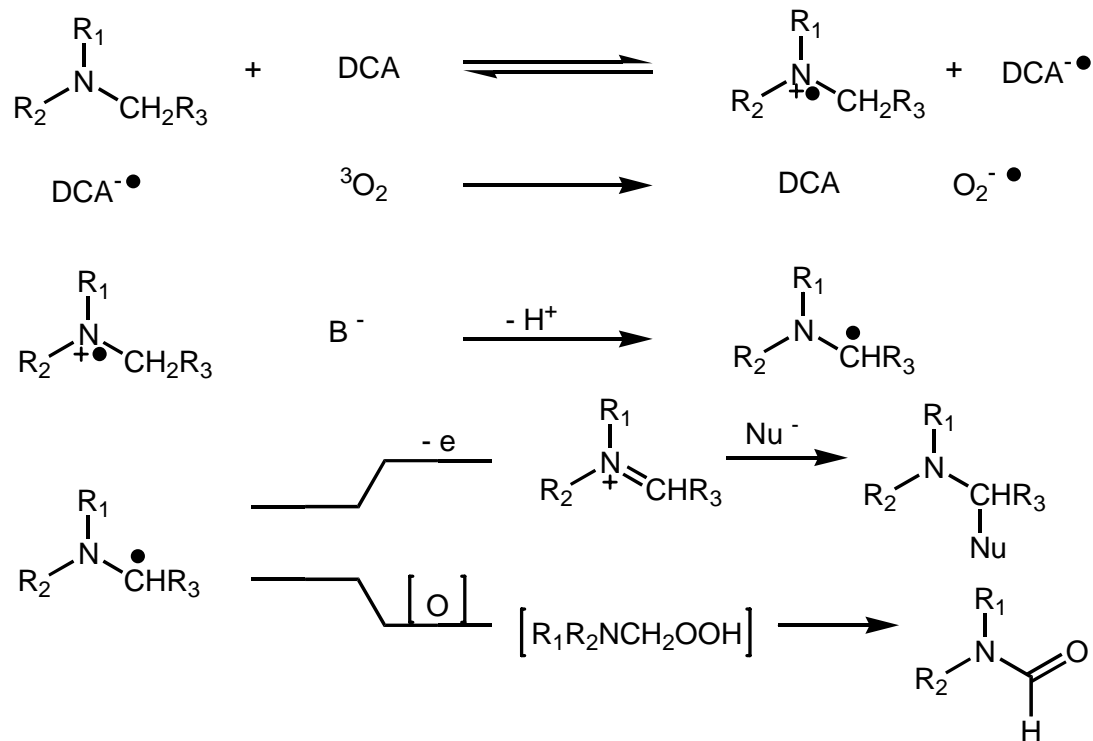
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- **Formation of Iminium Ions**
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Generation of Imininium Cations

Why are iminium cations important?

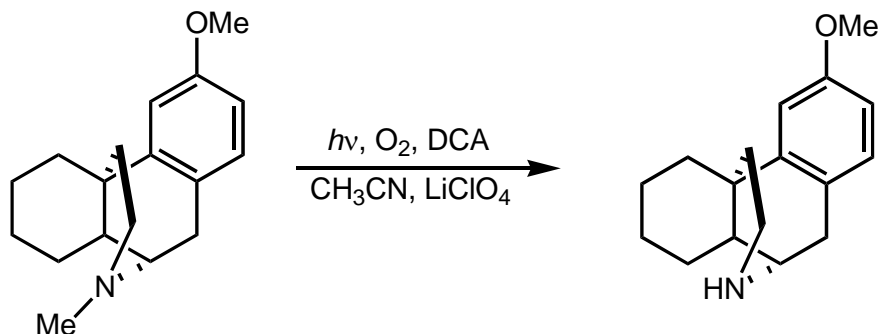
- Imininium cations are useful in the synthesis of nitrogen heterocycles which are present in biologically active alkaloids
- There is no convenient route to generate them

The Mechanism

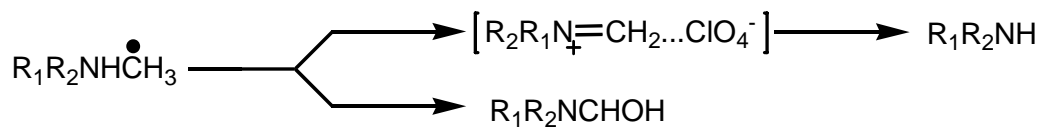
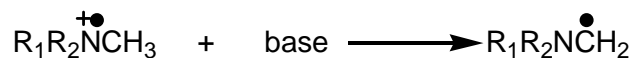
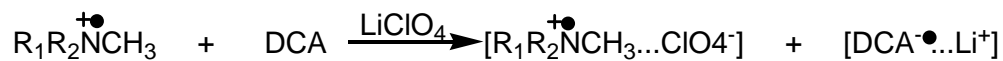
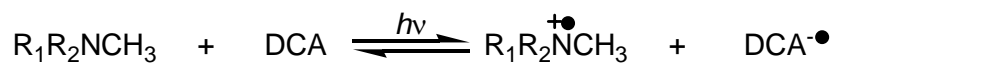


Photooxidative N-demethylation

Nordextromethorphan

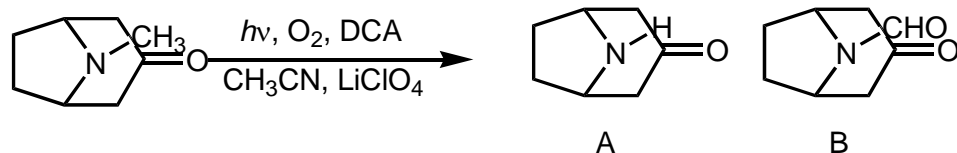


- The salt shifts theSSIP and CIP equilibrium
- The lifetime of the radicals can be as great as 15 times longer
- Allows for the formation of one type of product



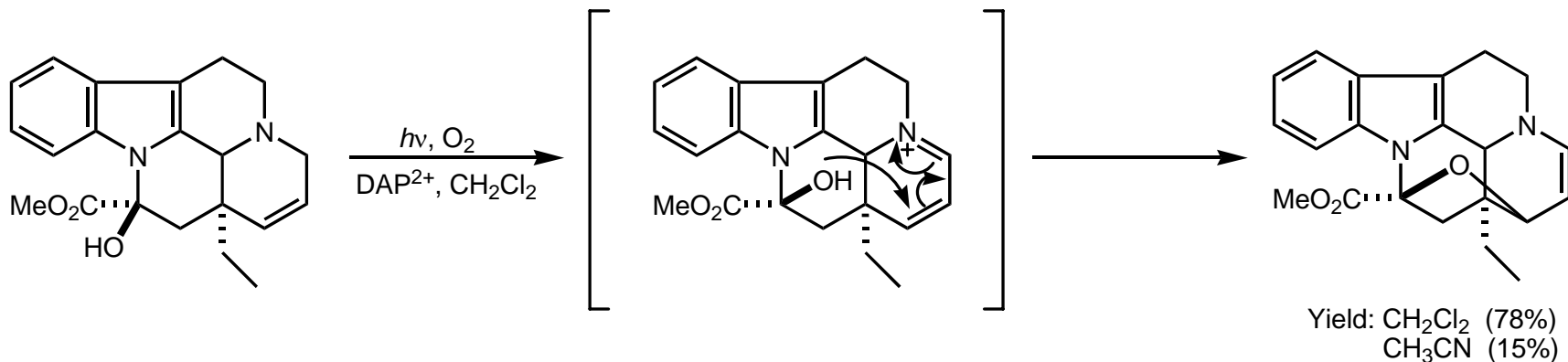
LiClO ₄ (equiv)	% Product A	% Product B
-	35	65
0.1	70	30
0.25	100	0
0.3	90	10
0.4	85	15
0.5	80	20
1	50	50
5	43	57

Salt Concentration Effect



Hemisynthesis of Criocerine

Formation of Criocerine from Δ^{14} -Vincine



Santamaria, J. *Pure & Appl. Chem.* **1995**, 67, 141.

Solvent Effects

- PET reactions are solvent dependent!!!
- SSIP more stable in polar solvents which separate to form FRIP's
- SSIP's favored by 0.98 eV in MeCN over hexanes
- Only CIP's can be formed in nonpolar media
- Reaction efficiency can be lost in nonpolar solvents due to greater amounts of reverse electron transfer

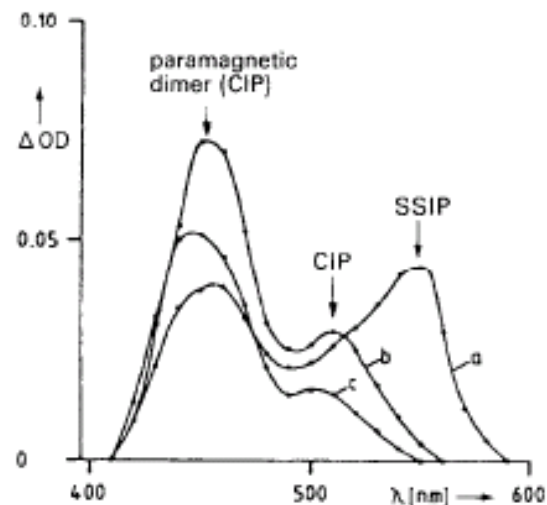


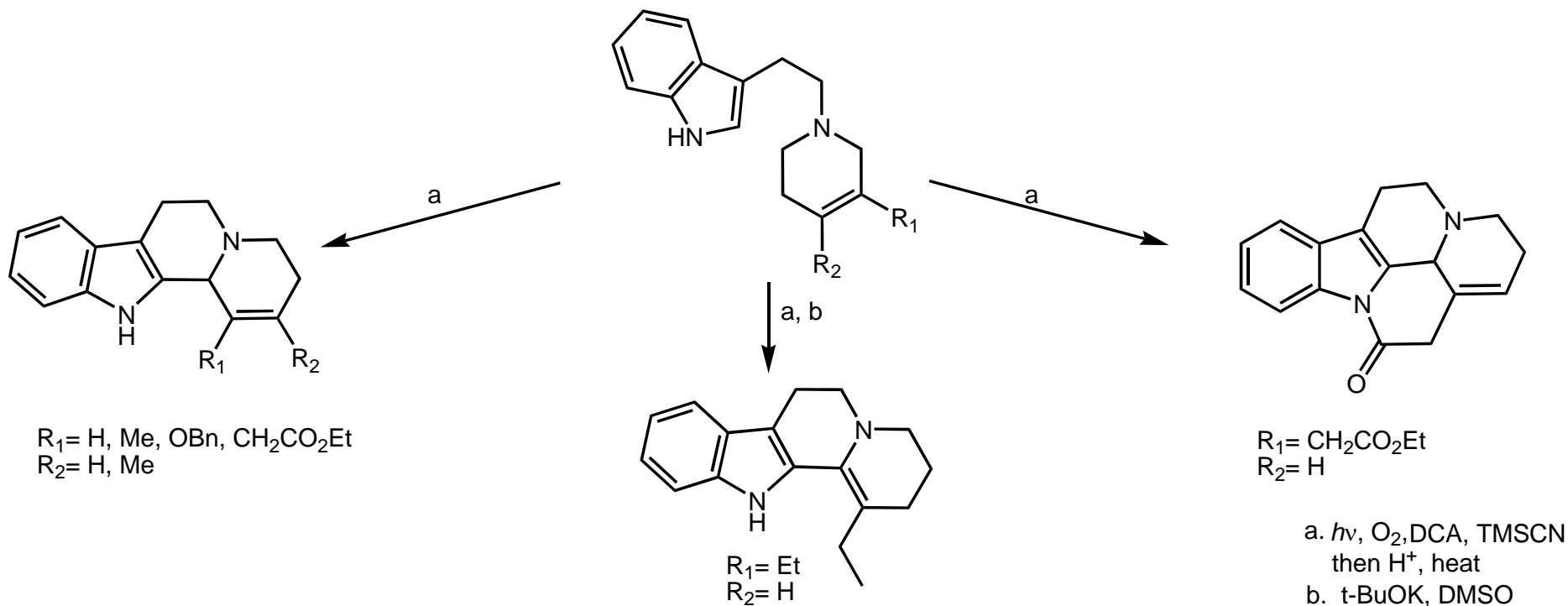
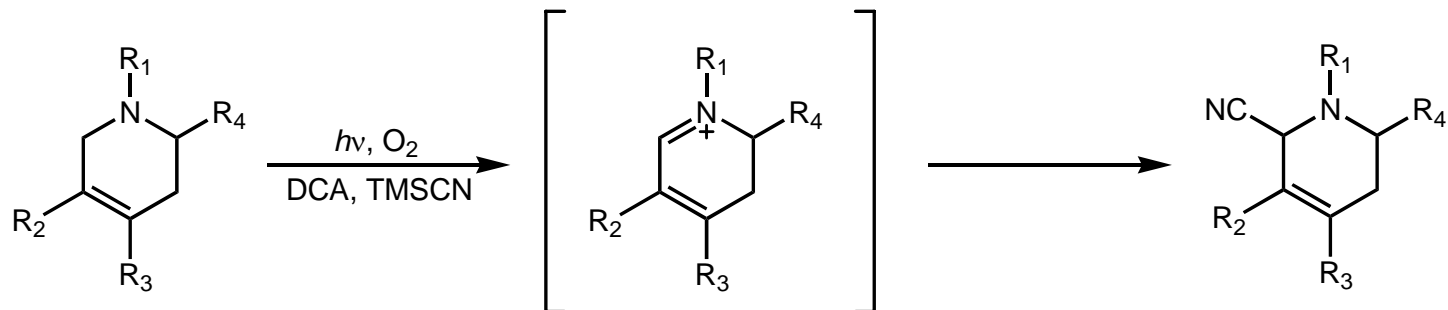
Fig. 7. Transient absorption spectra (ΔOD = absorption difference) 100 μs after flash photolytic excitation of **1** in the presence of tetramethyl-1,3-dioxole **2** in various solvents (from [60]). a) Acetonitrile. b) Benzene. c) Cyclohexane.

Mattay, J. *Synthesis* **1989**, 233.

Mattay, J. *Angew. Chem. Int. Ed.* **1987**, 26, 825.

Synthesis of Indoline Alkaloid Precursors

Formation of α -amino nitriles



$R_1 = \text{H, Me, OBn, CH}_2\text{CO}_2\text{Et}$
 $R_2 = \text{H, Me}$

$R_1 = \text{Et}$
 $R_2 = \text{H}$

$R_1 = \text{CH}_2\text{CO}_2\text{Et}$
 $R_2 = \text{H}$

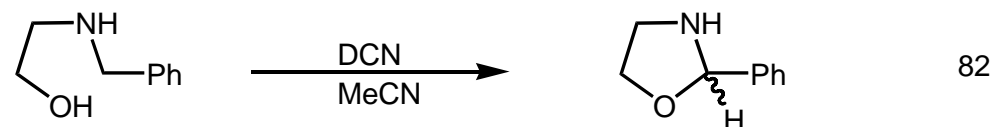
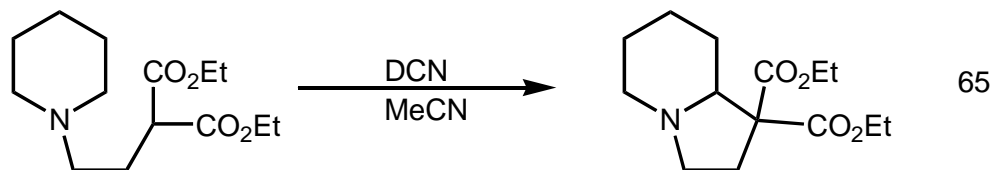
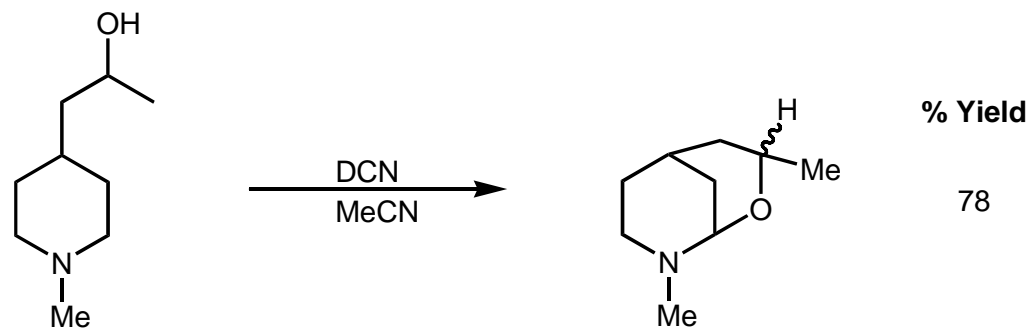
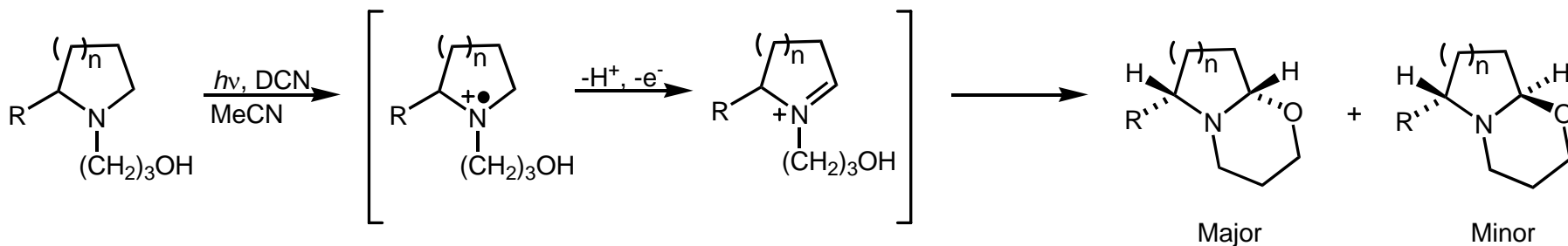
a. $h\nu, O_2, DCA, TMSCN$
then H^+ , heat
b. $t\text{-BuOK, DMSO}$

Outline

- The Basics
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- **Reactions Involving Iminium Ions**
- Arene Acceptor Reactions
- Cyclizations
- Amine Reductions

In Situ Trapping of Iminium Cations

Intramolecular Cyclization



Major

Minor

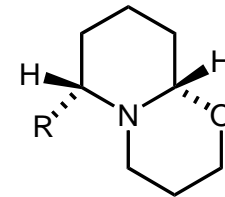
%Yield

n = 1, R = n-Butyl 96 : 4

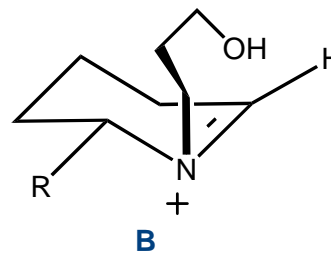
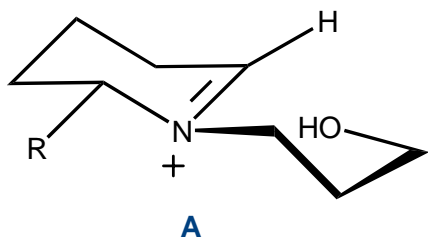
n = 2, R = n-Butyl 95 : 5

n = 2, R = Me 93 : 7

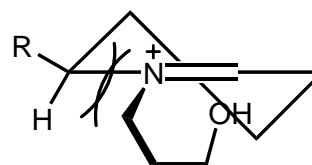
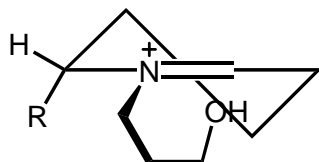
Stereochemical Explanation



The authors propose...



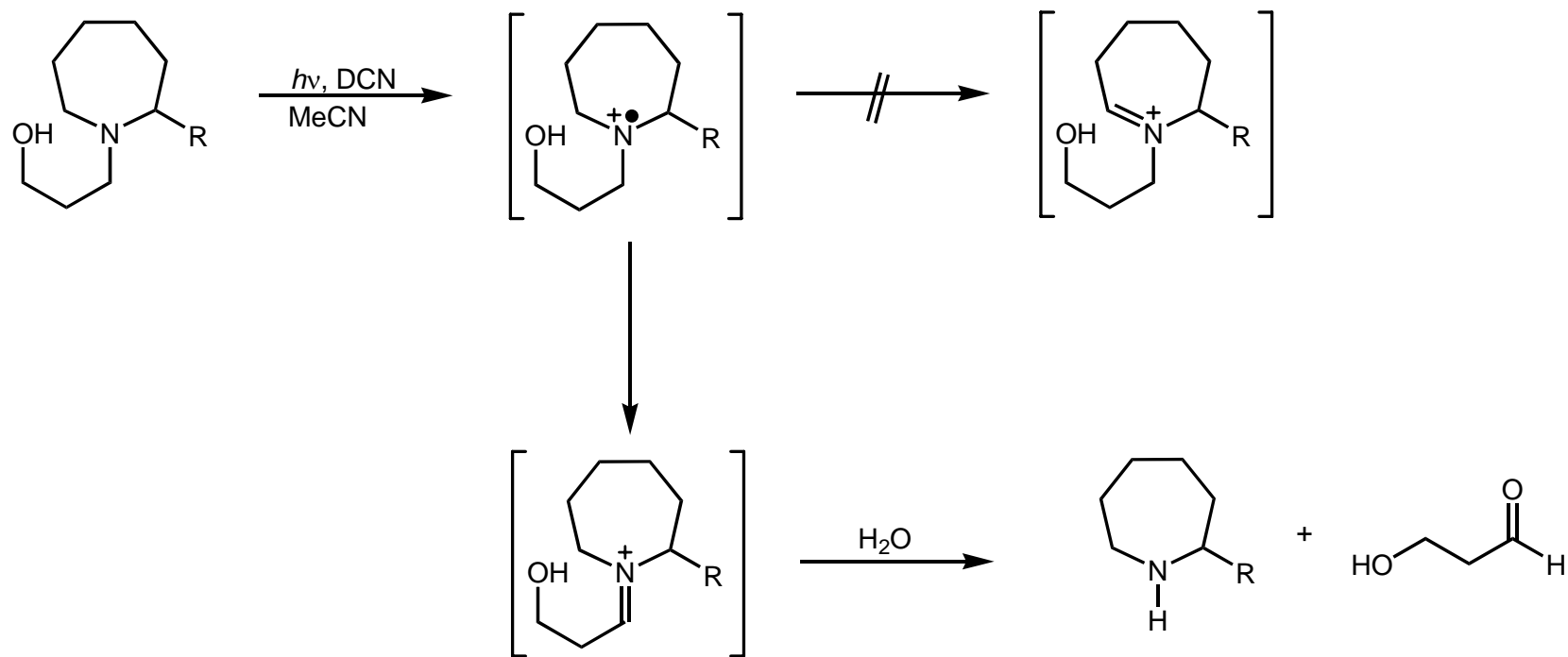
But perhaps there is a better explanation...



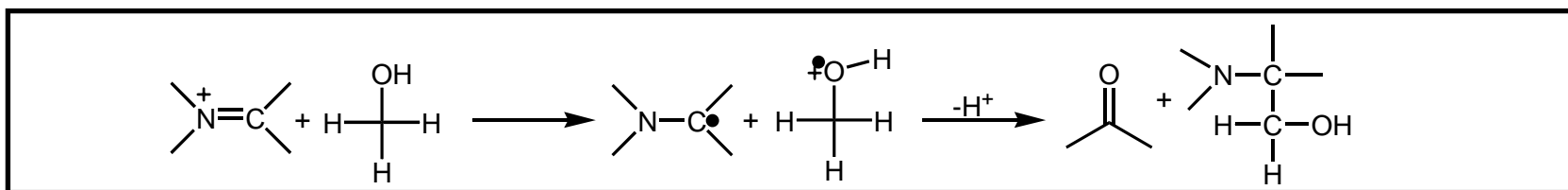
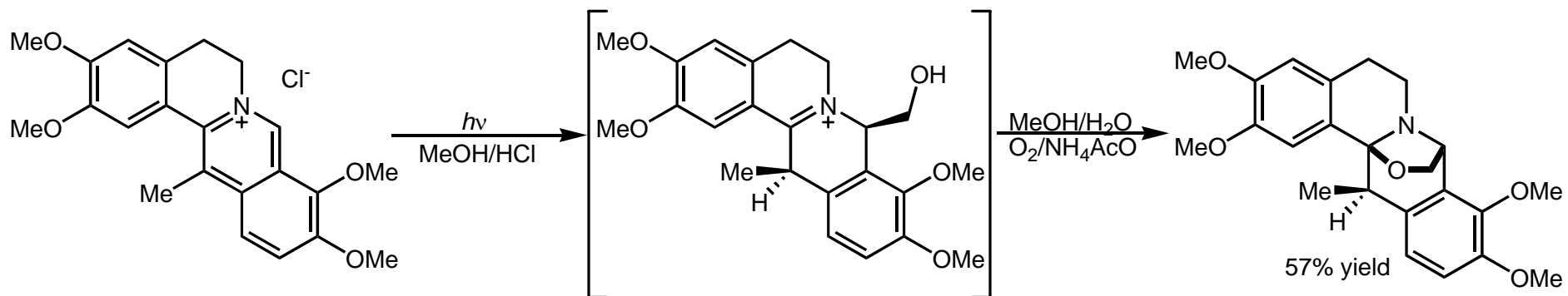
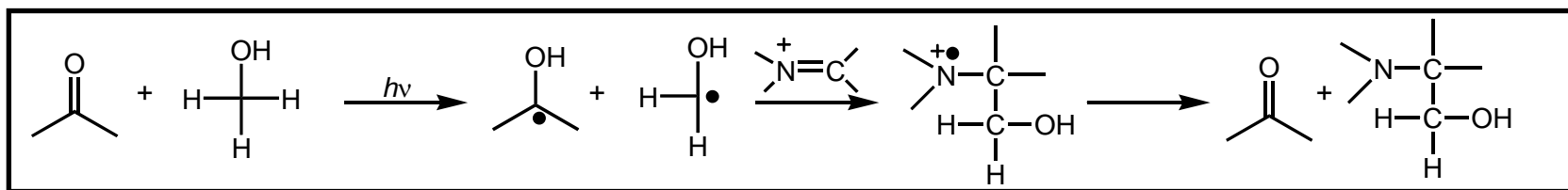
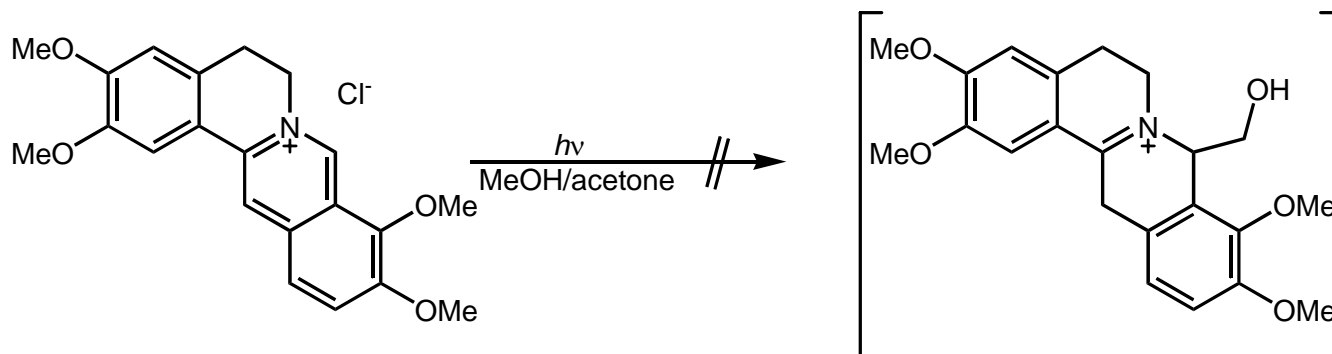
A 1,2 Strain

Formation of Larger Rings

Formation of An Exocyclic Iminium Cation

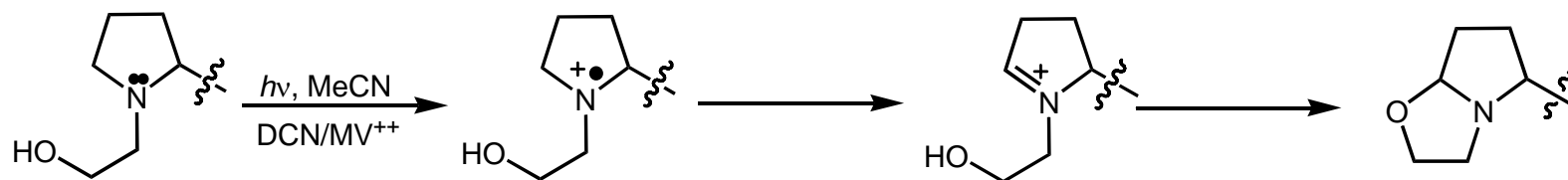
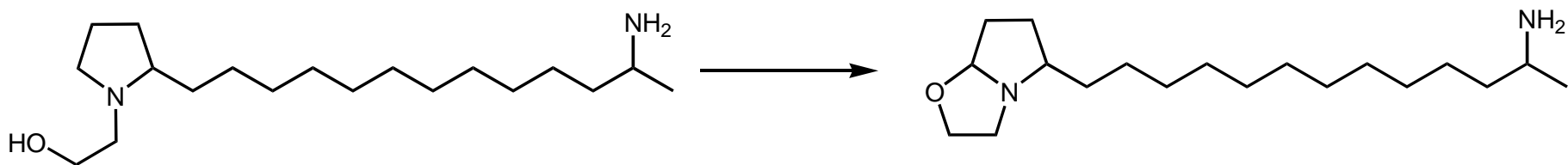


Formation (\pm)-Solidaline



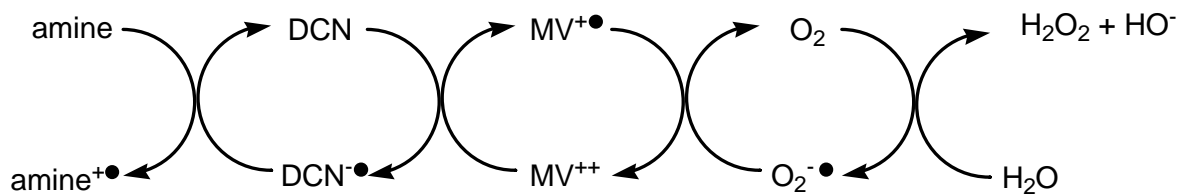
Formation of Pyrrolidinoxazolidine Alkaloids

Synthesis of the Major Defensive Constituent of the Squash Beetle



Radford, P.; Attygalle, A.; Meinwald, J. *J. Nat. Prod.* **1997**, *60*, 755.

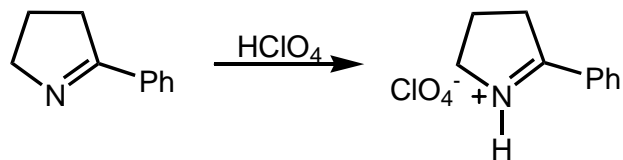
Methyl Viologen (MV^{++}): an electron relay source



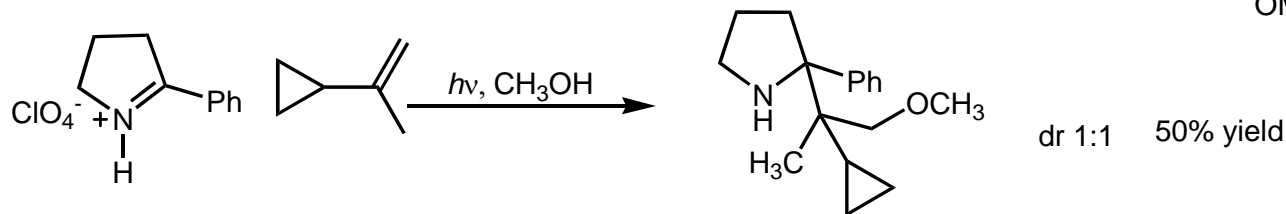
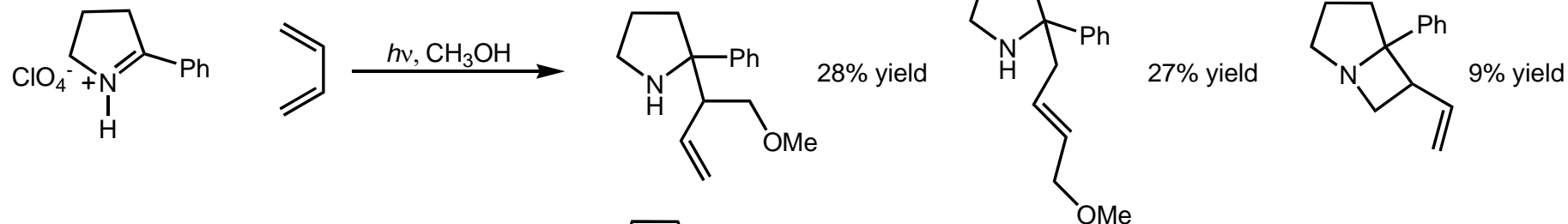
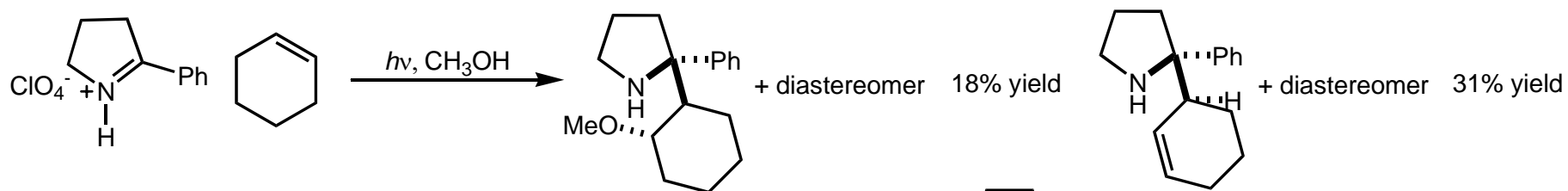
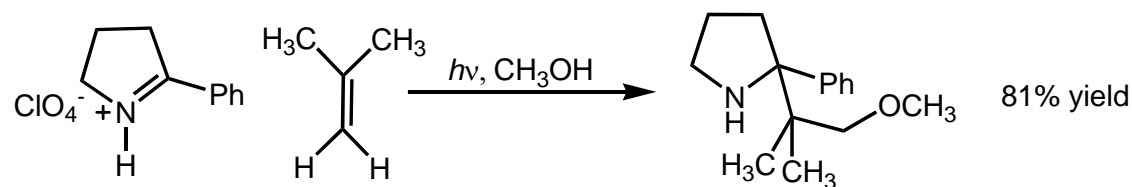
Pandey, G.; Kumaraswamy, G.; Reddy, P. *Tetrahedron* **1992**, *48*, 8295.

PET Involving Iminium Salts

Studies using 2-phenyl-1-pyrrolinium perchlorate

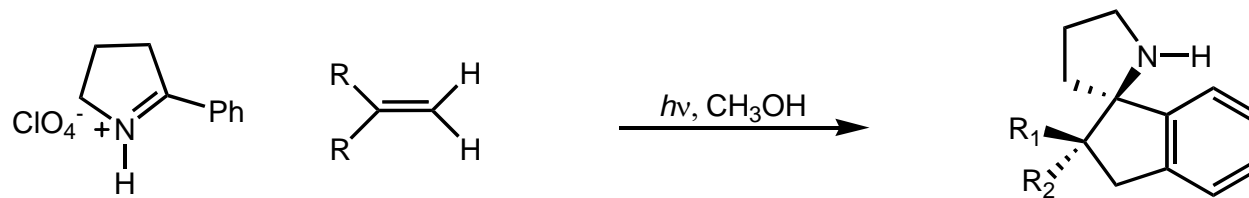


Photoadditions of Electron Rich Olefins



Photoaddition to Electron Poor Olefins

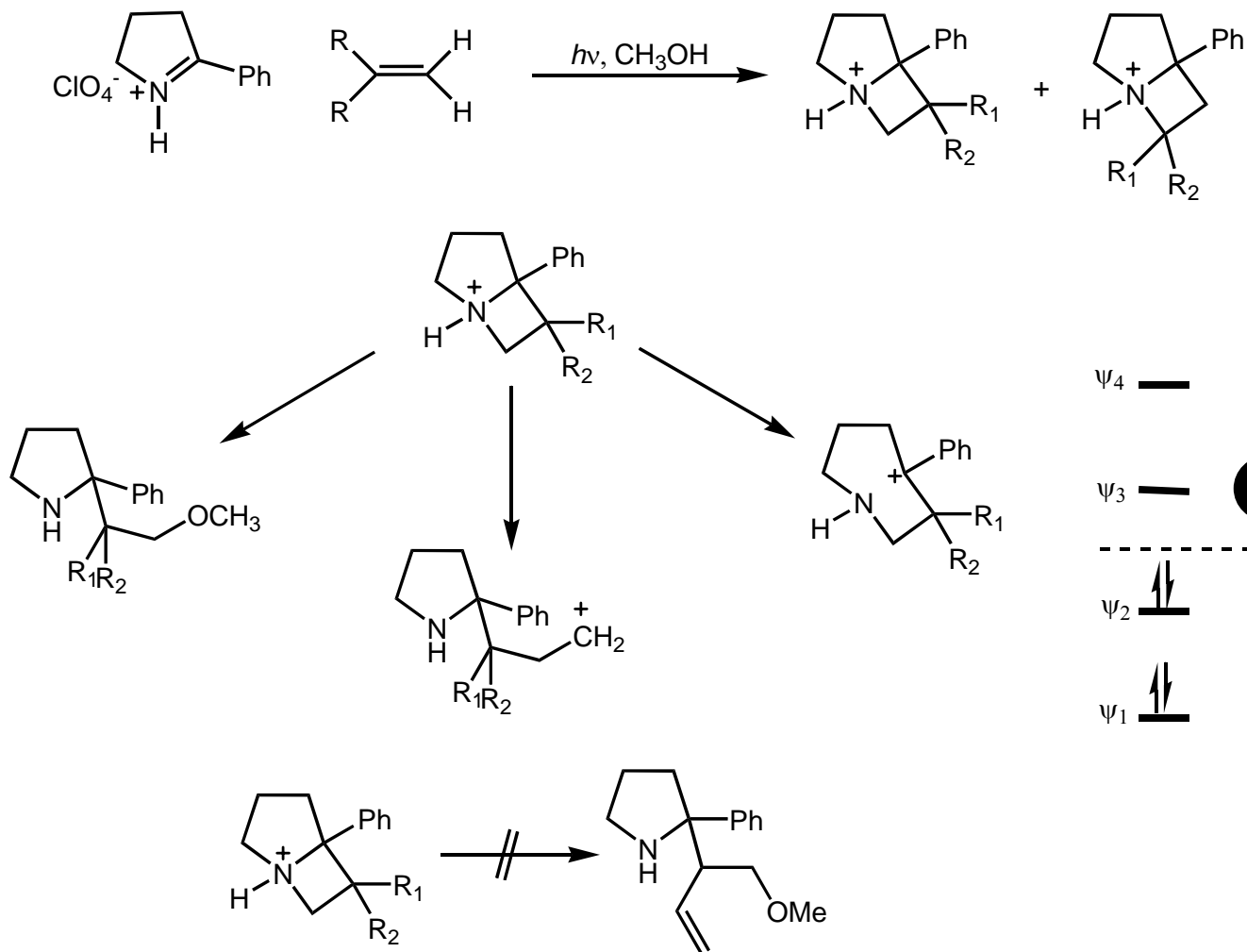
Substituent Effects



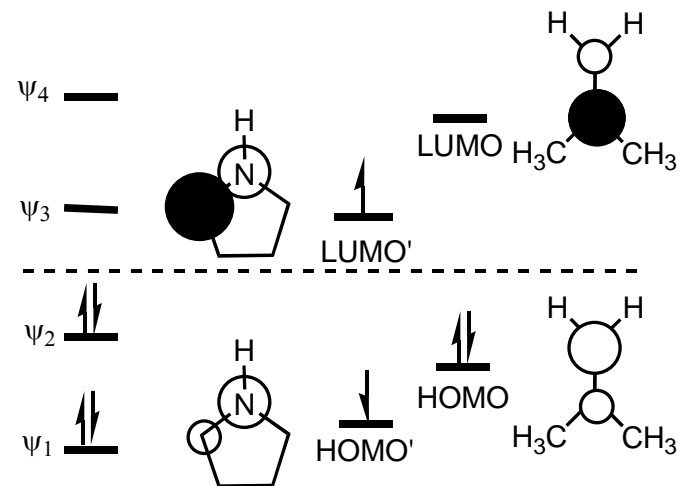
R_1	R_2	Yield
CN	H	44% (1.5:1)
H	CN	
CO_2CH_3	H	50-52% (1:1)
H	CO_2CH_3	
CO_2CH_3	CH_3	54% (1:1)
CH_3	CO_2CH_3	

A [2+2] Cycloaddition?

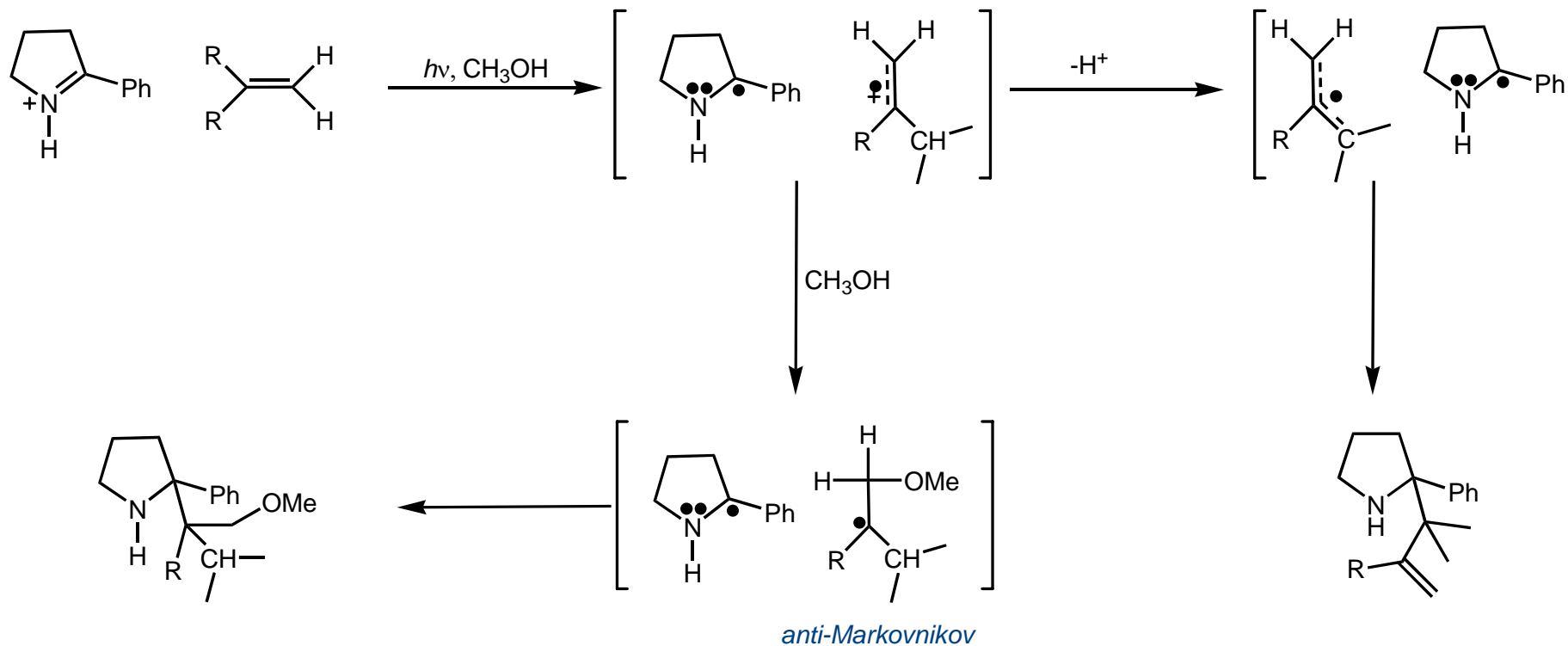
Mechanistic Explanation



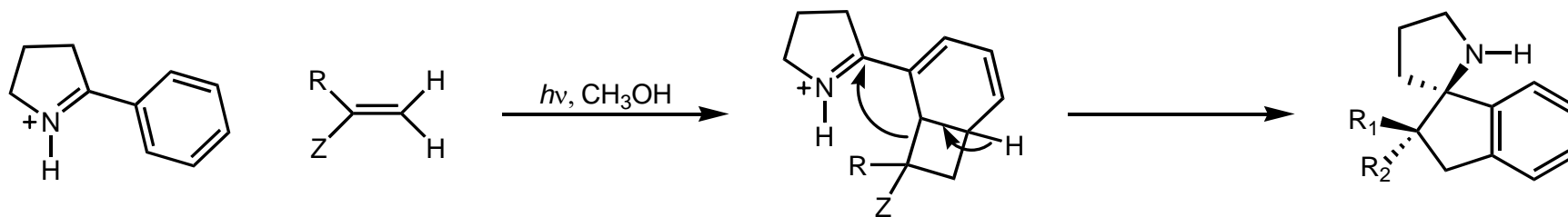
Regiochemistry



Electron Transfer Mechanism

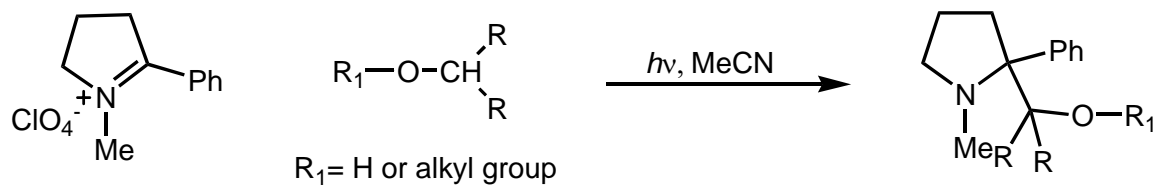


Cycloaddition Mechanism

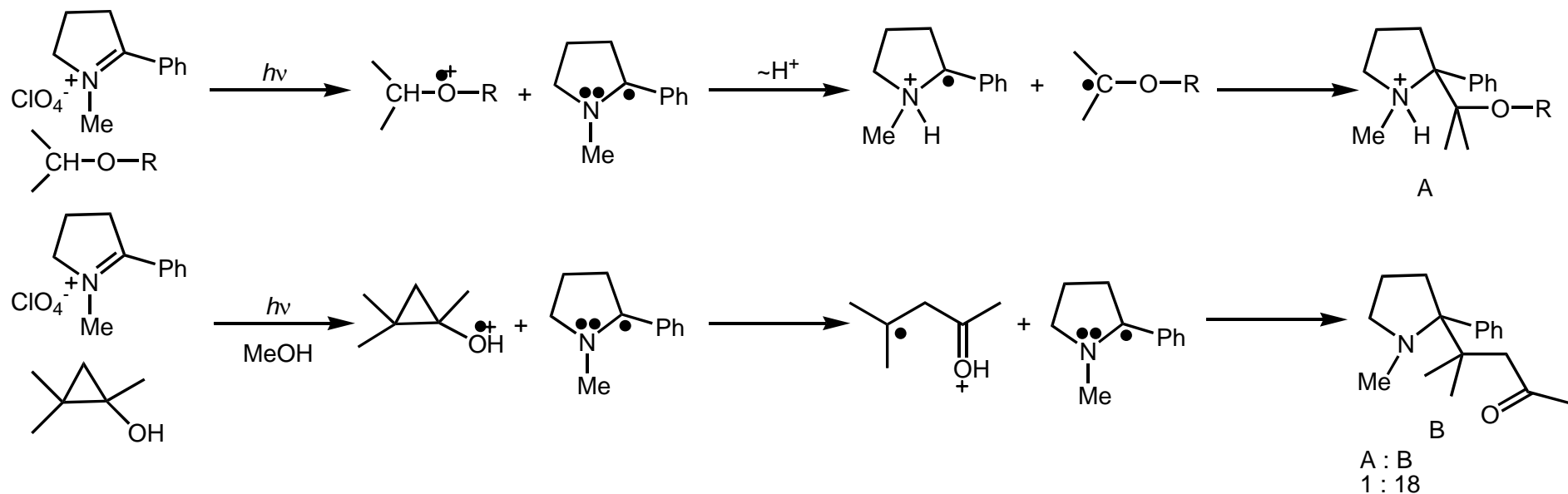


PET Involving Alcohols and Ethers

Substrate Scope

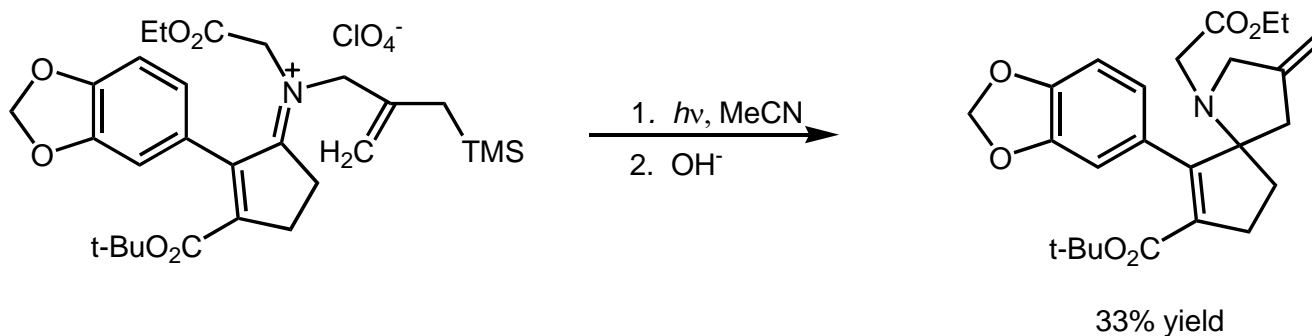
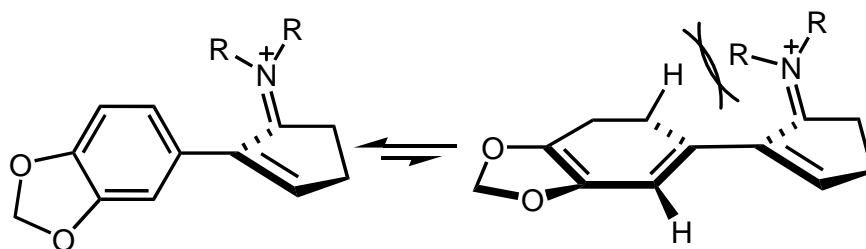
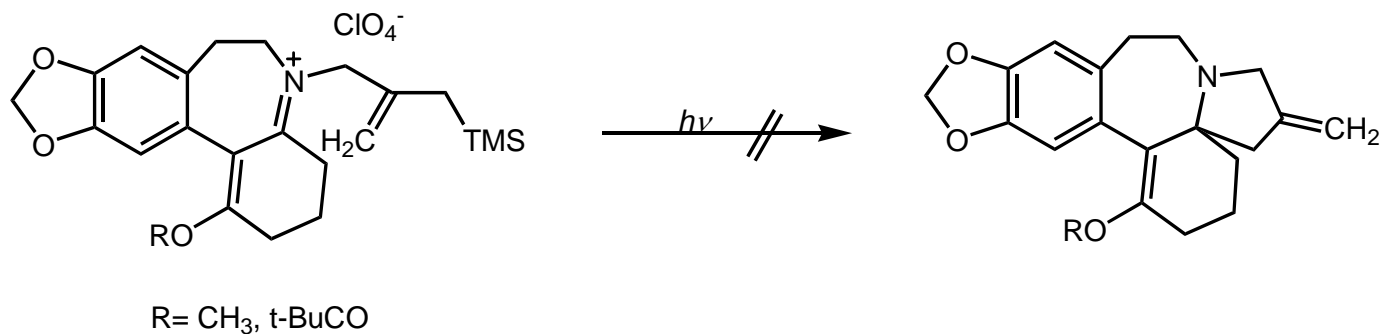


Mechanistic Pathways

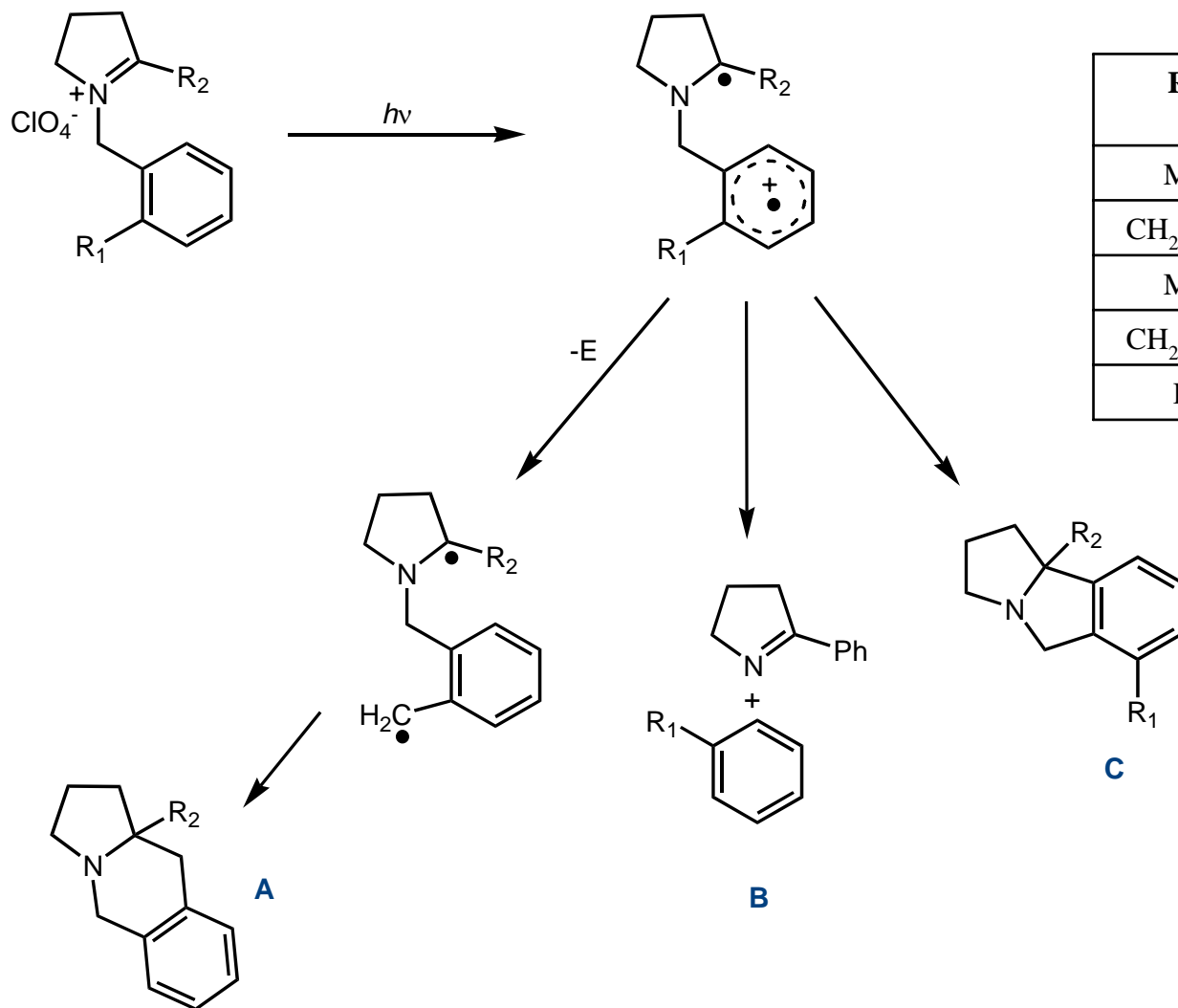


Model Studies to Aid in the Synthesis of Harringtonine Alkaloids

Spirocyclic Amine Synthesis

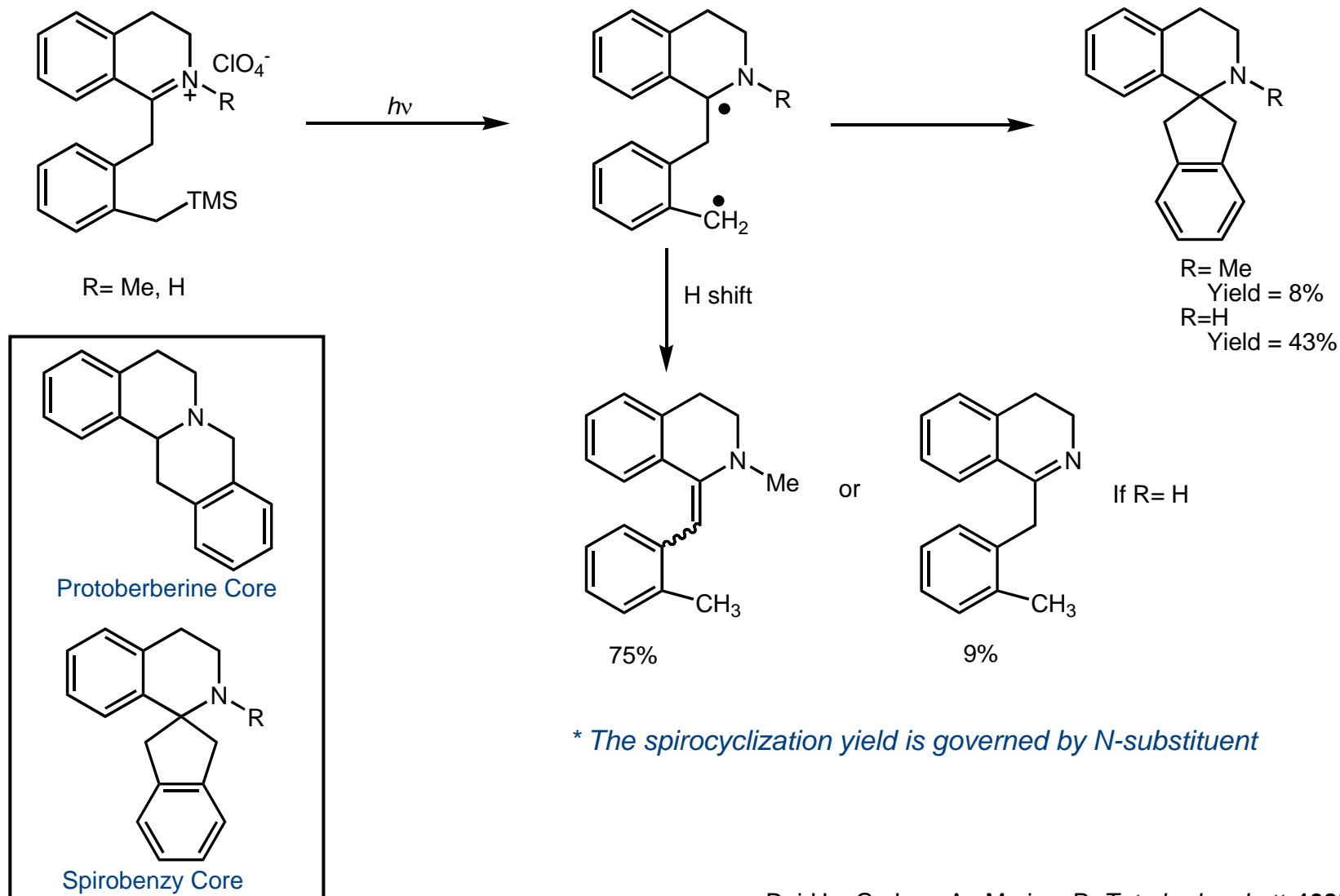


PET In Arene-Iminium Salt Systems



R_1	R_2	Product (Yield)
Me	Ph	A (18), B (15)
CH_2TMS	Ph	A (>40)
Me	Me	C (90)
CH_2TMS	Me	A (70)
H	Me	C (90)

Steps Towards the Synthesis of Protoberberine and Spirobenzyl Isoquiniline Alkaloids

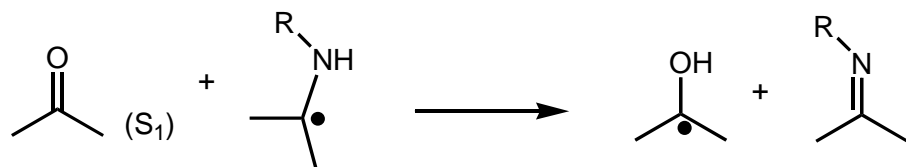
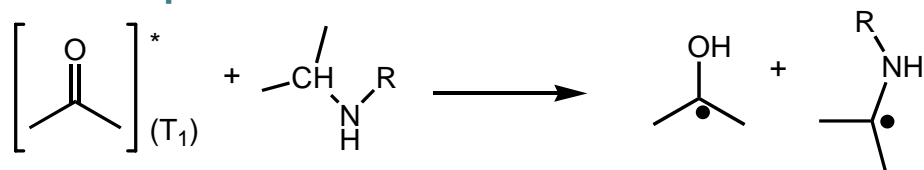


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- **Cyclizations**

Photoreduction Using Amines

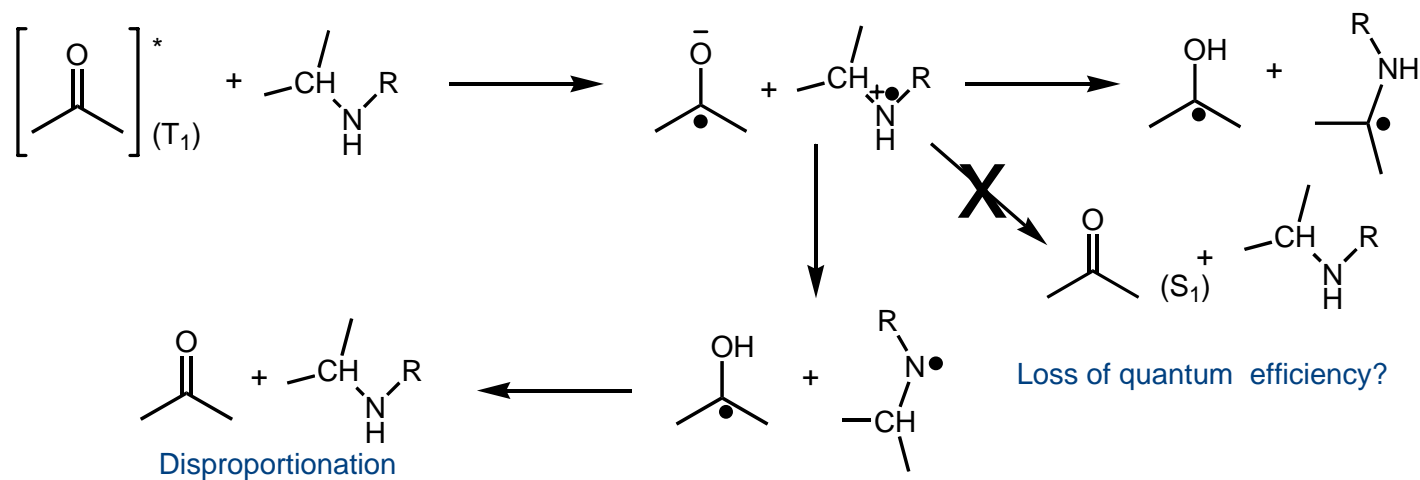
Initial Proposed Mechanism



- Amines vs. Alcohols:

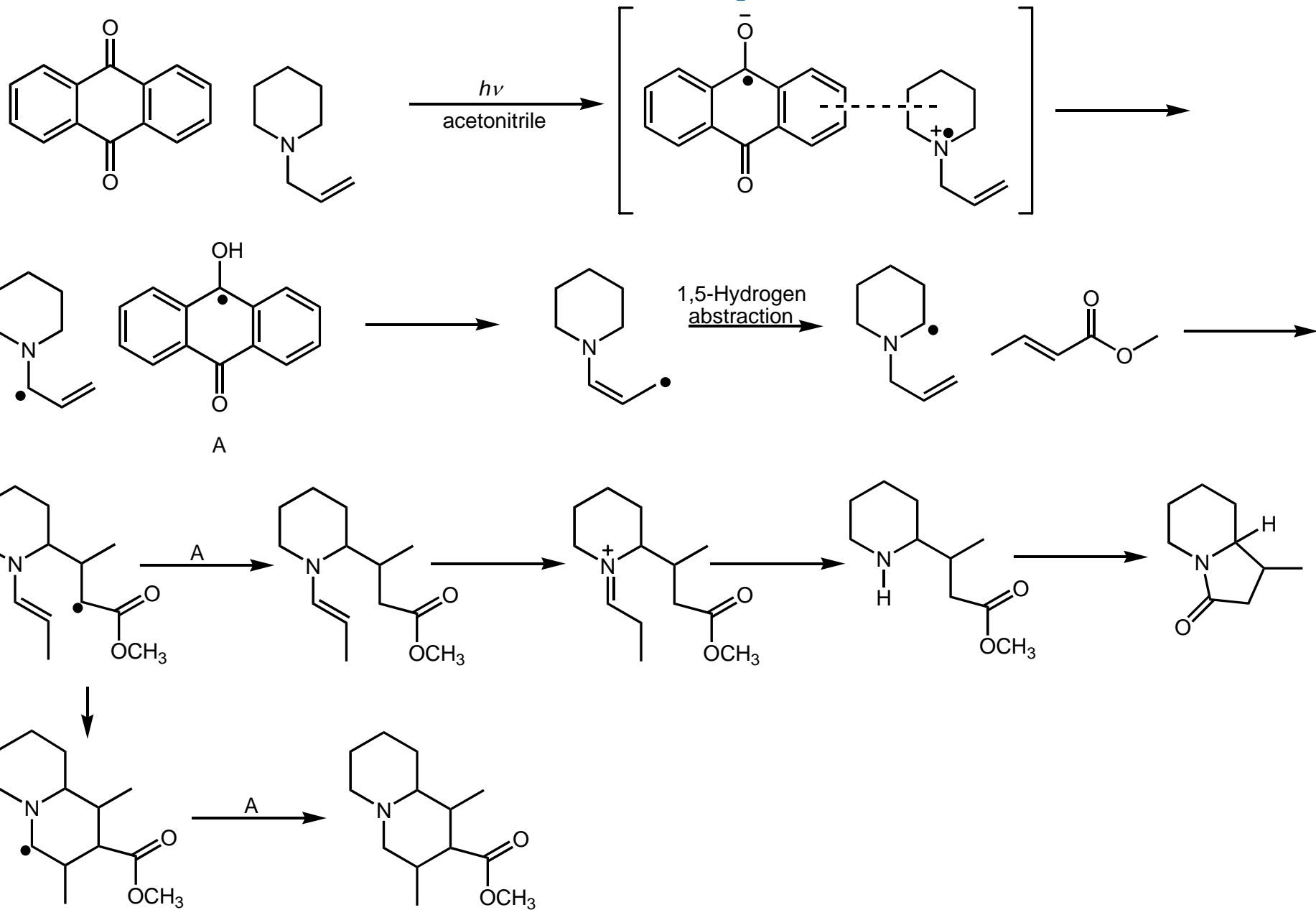
- Rate constants are much higher for amine reduction
- Amines may reduce π, π^* states and charge transfer triplets which alcohols generally do not do

Revised Mechanism

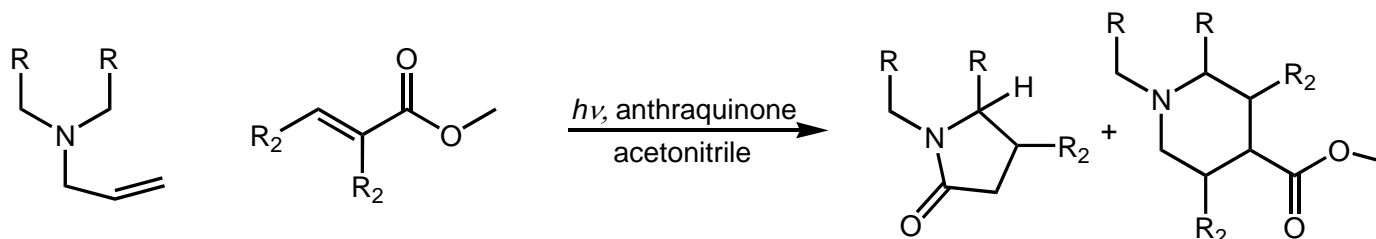


- N centered radicals lead to disproportionation, not C centered radicals
- Secondary amines have lower quantum efficiency than primary amines
- N-H bond strengths may play a role (methyl amine N-H = 103 kcal/mol, dimethyl amine N-H = 96 kcal/mol)

Mechanistic Explanation

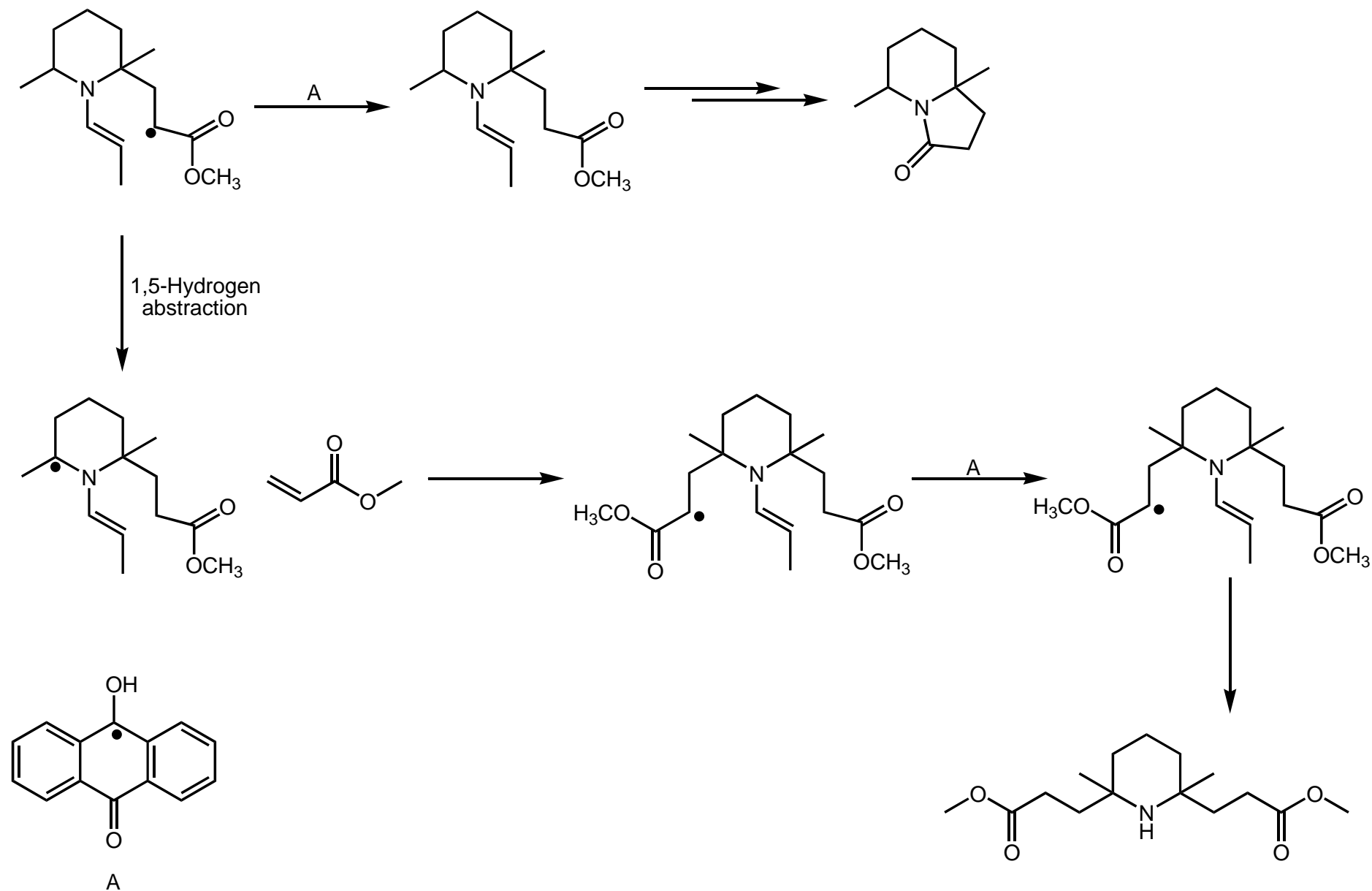


Lactam Formation Using PET



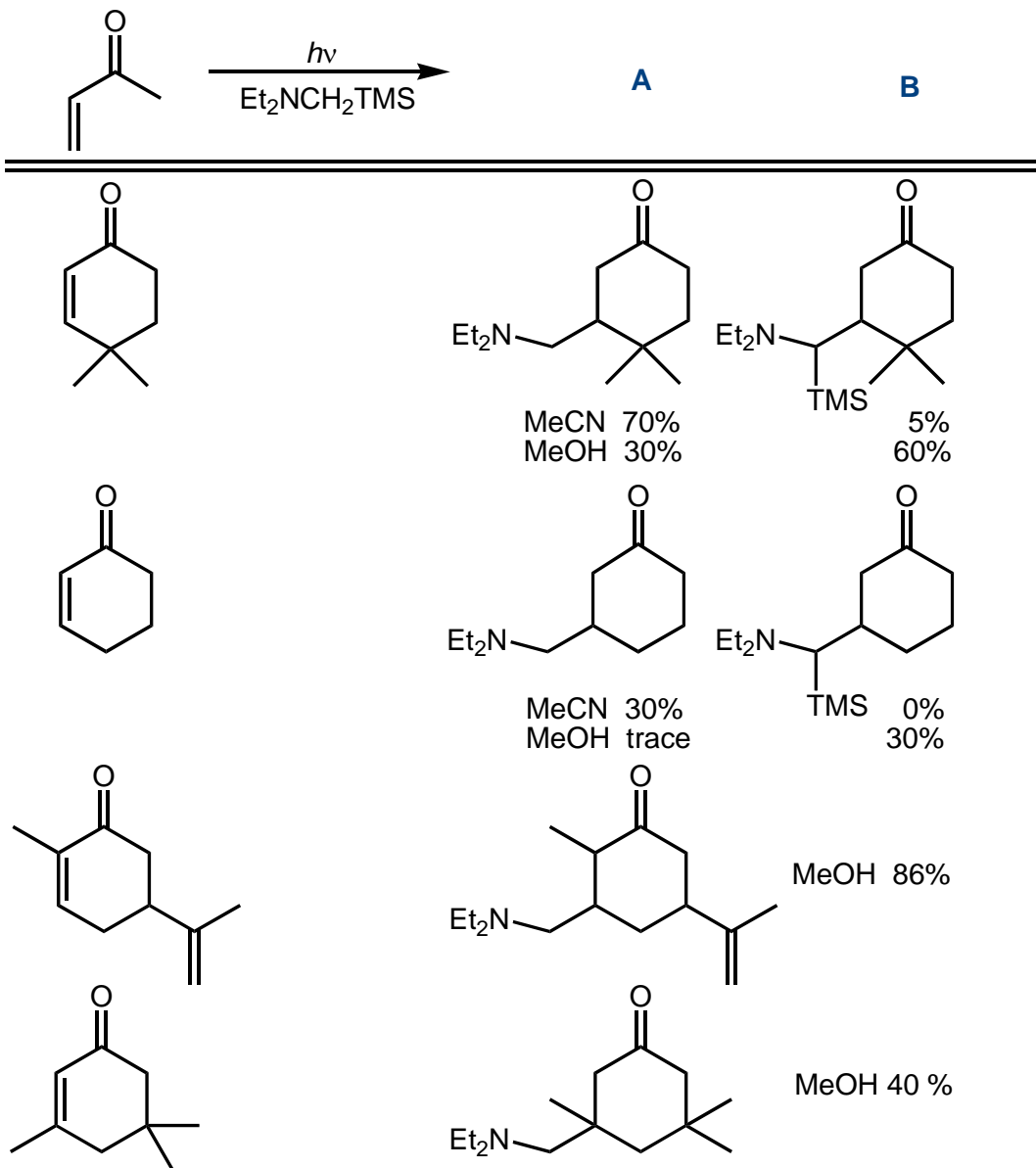
Reaction 1	Reaction 2	Reaction 3	Reaction 4	Reaction 5	% Yield
					40 : 15
					50 : 10
					60
					20
					30

Olefin Addition Products

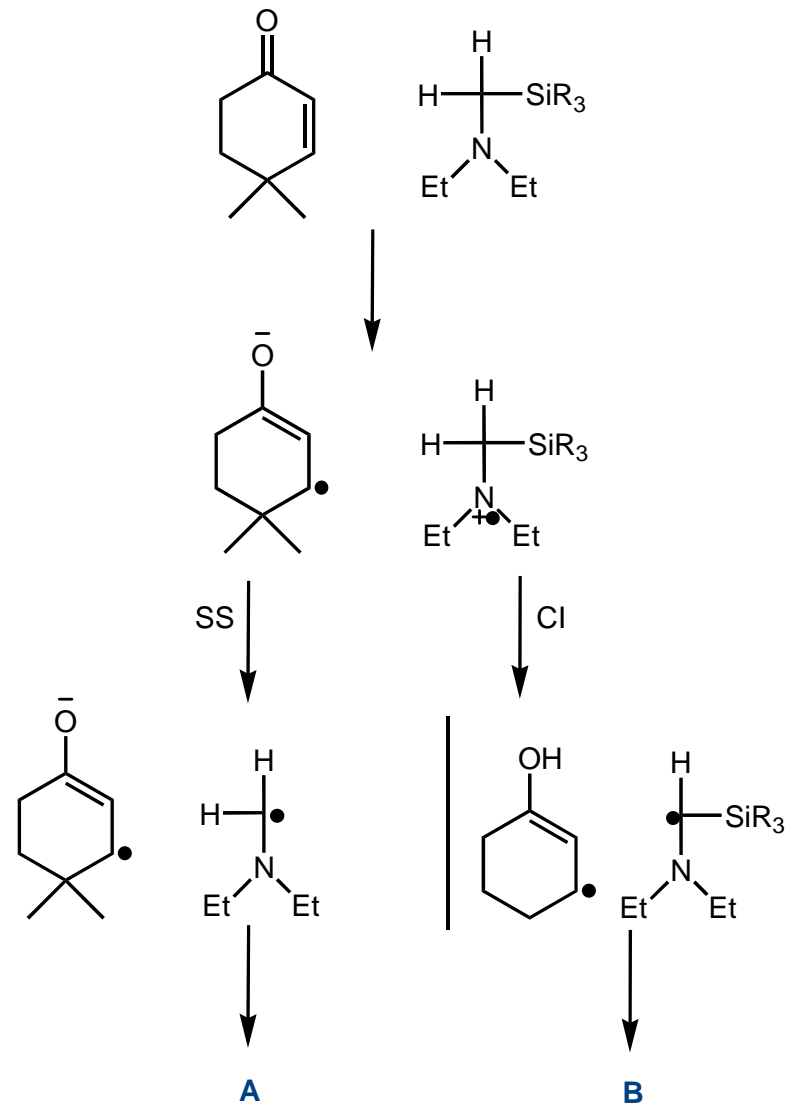


PET in α -Silylamine-Cyclohexenone Systems

α -Silyl Tertiary Amine Donors



Mechanism

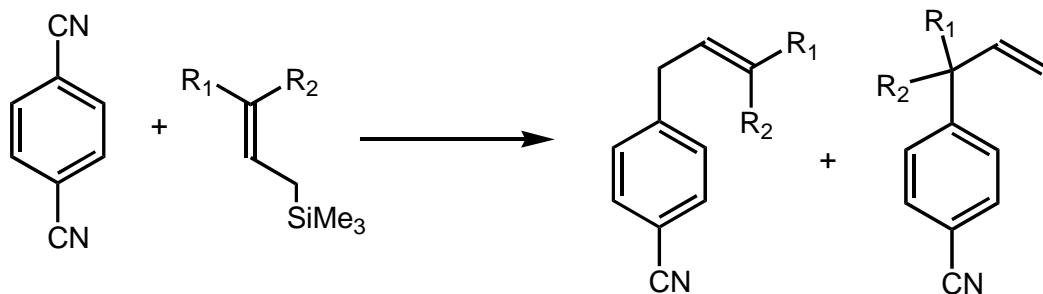


Outline

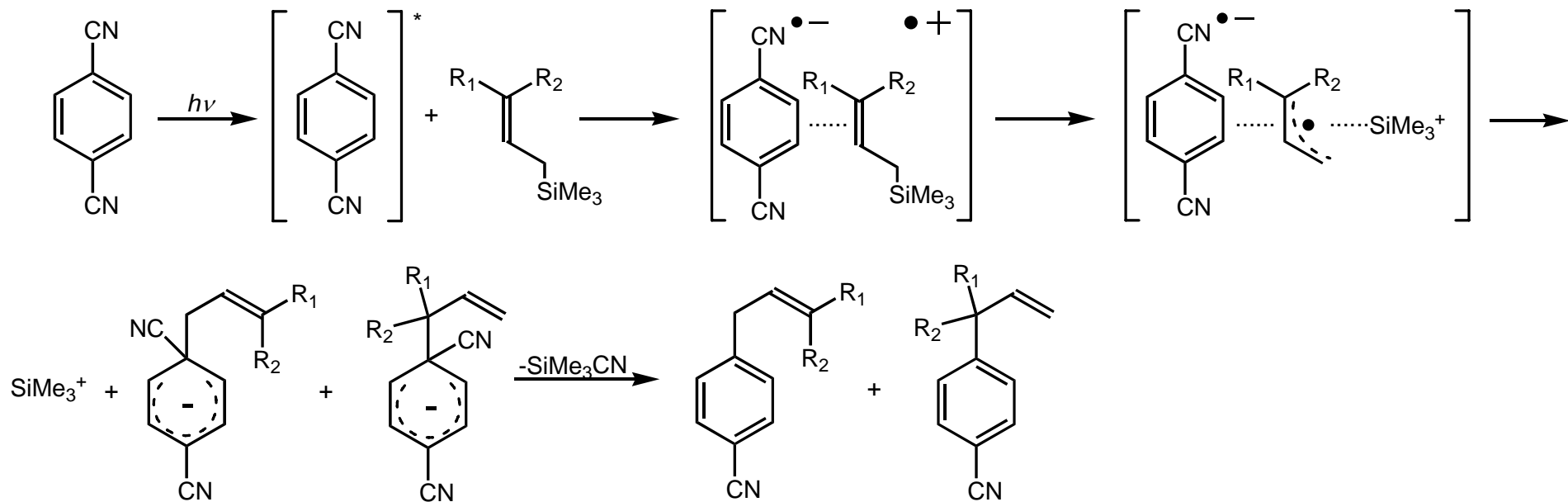
- The Basics
- Formation of Iminium Ions
- Reactions Involving Iminium Ions
- Carbonyl Reductions Using Amines
- **Arene Acceptor Reactions**
- Cyclizations

Photosubstitution of Dicyanobenzenes

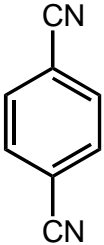
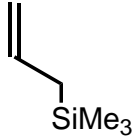
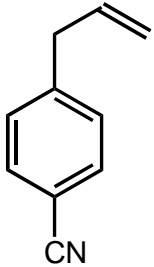
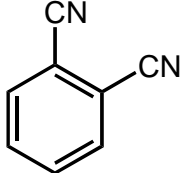
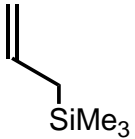
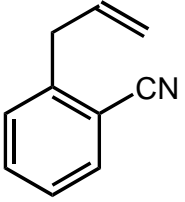

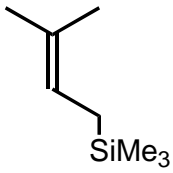
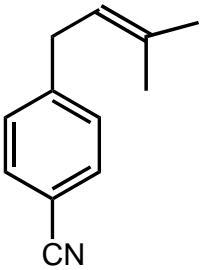
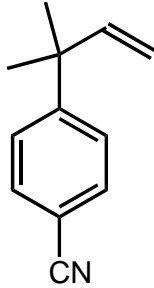
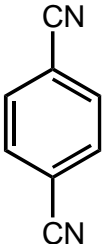
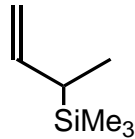
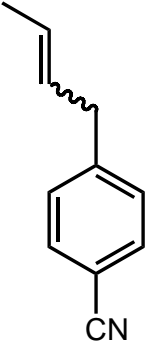
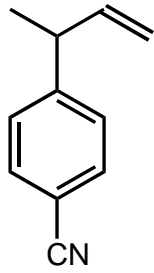
Formation of Substituted Cyanobenzenes



Proposed Mechanism

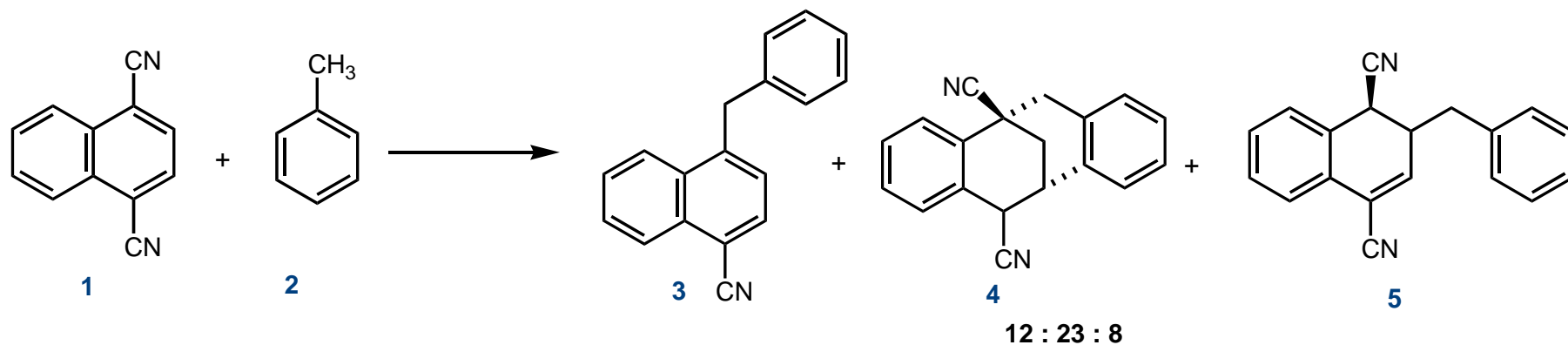


Photosubstitution of Dicyanobenzenes by Allylic Silanes

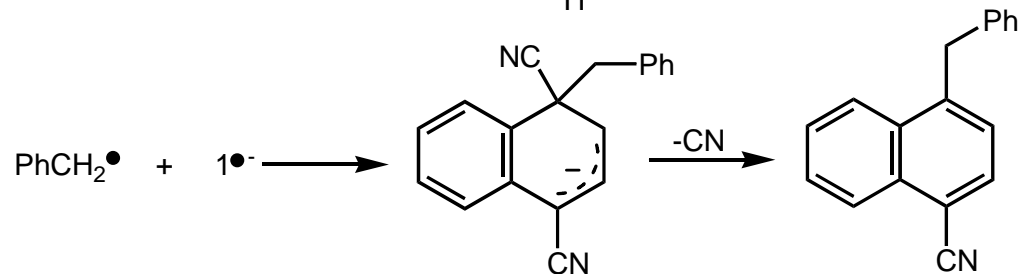
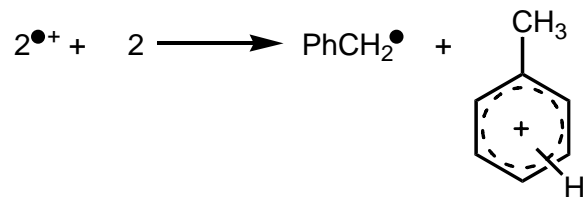
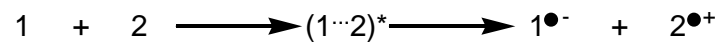
Aromatic Nitrile	Allylic Silane	Product(s)	% Yield	% Conversion
			66	100
			67	70
		 	91	100
		 	80	100

PET Studies Involving Cyano Aromatic Compounds

Formation of Benzylated Cyanonaphalenes

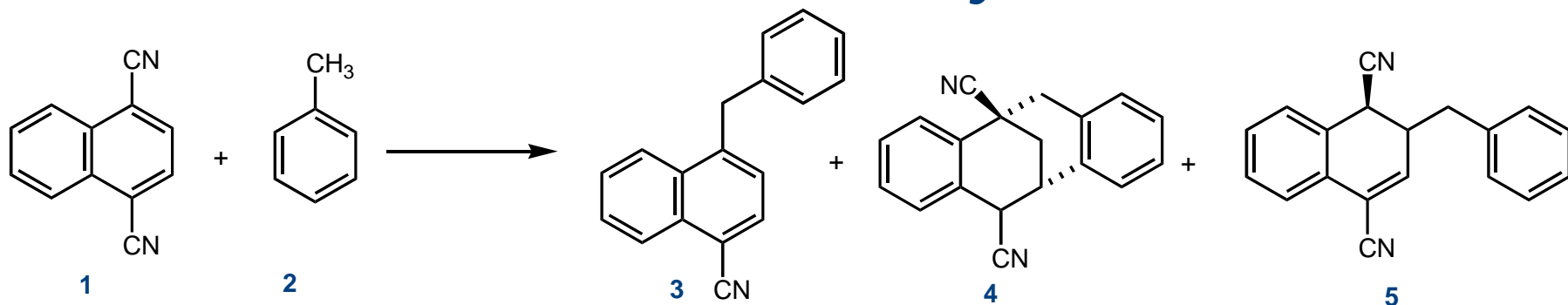


Proposed Mechanistic Pathway to 3

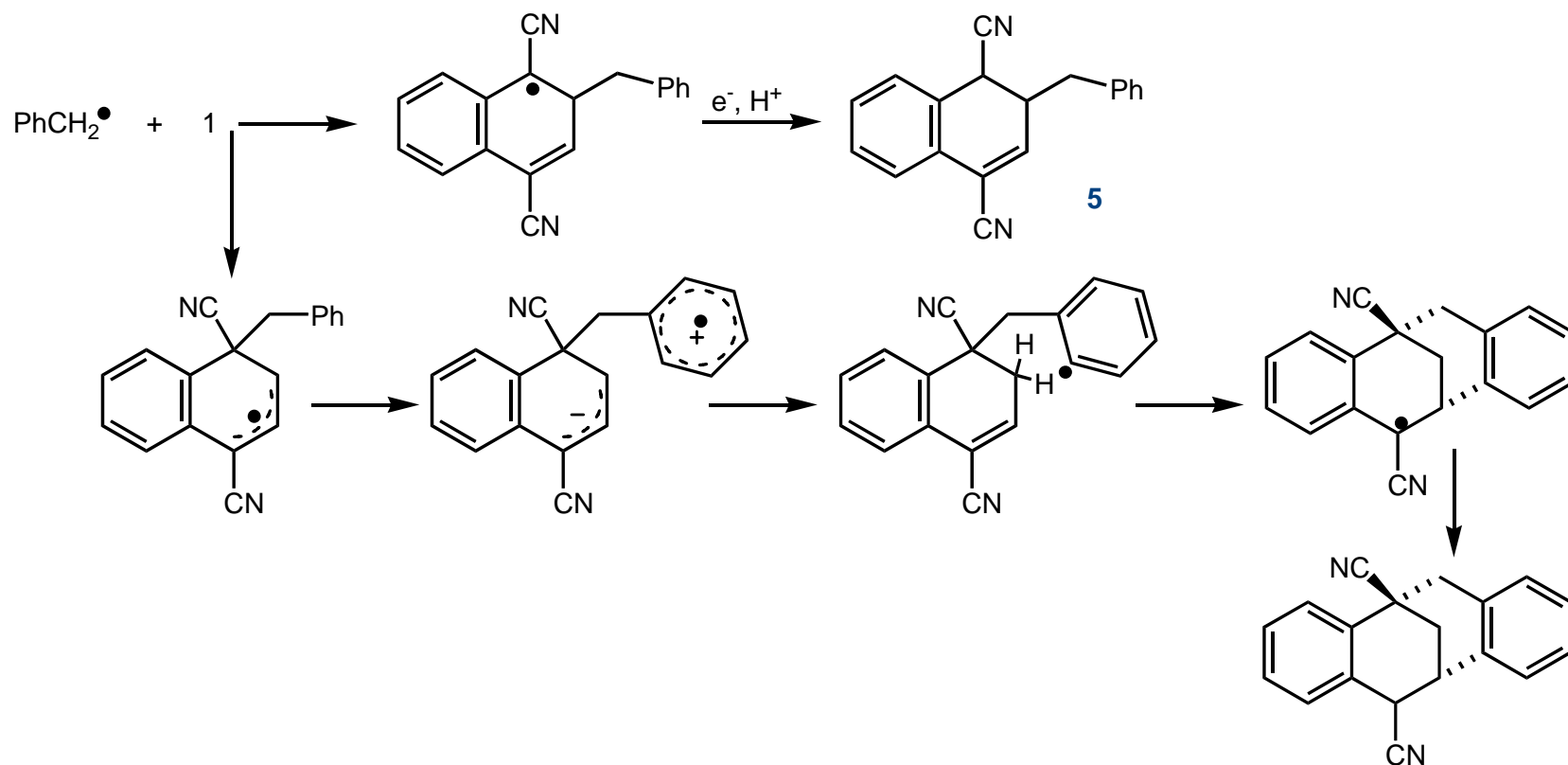


3

Photosubstitution of Dicyanobenzenes

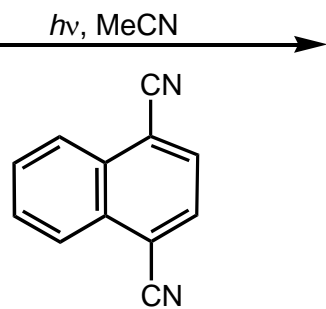
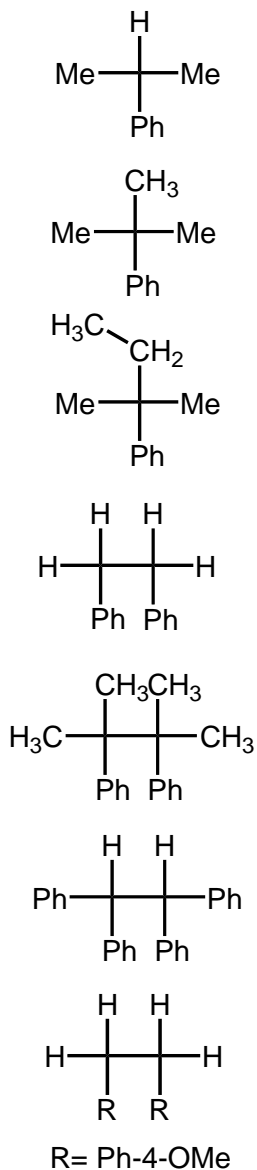


Mechanistic Pathway to Products 4 and 5



PET Involving NDN, Alkylbenzoates and Bibenzyls

Substrate Scope



Products

1 and 2
 $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Me}$

No Reaction

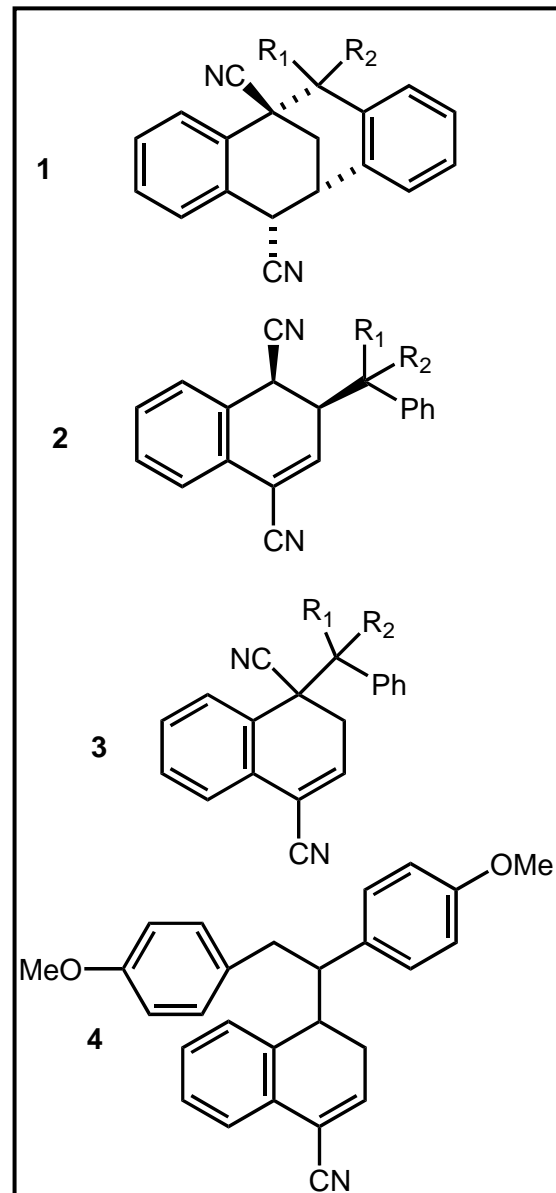
1 and 3
 $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Me}$

1, 2, 3, 4 and dimer
 $\text{R}_1 = \text{H}, \text{R}_2 = \text{CH}_2\text{Ph}$

2
 $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Me}$

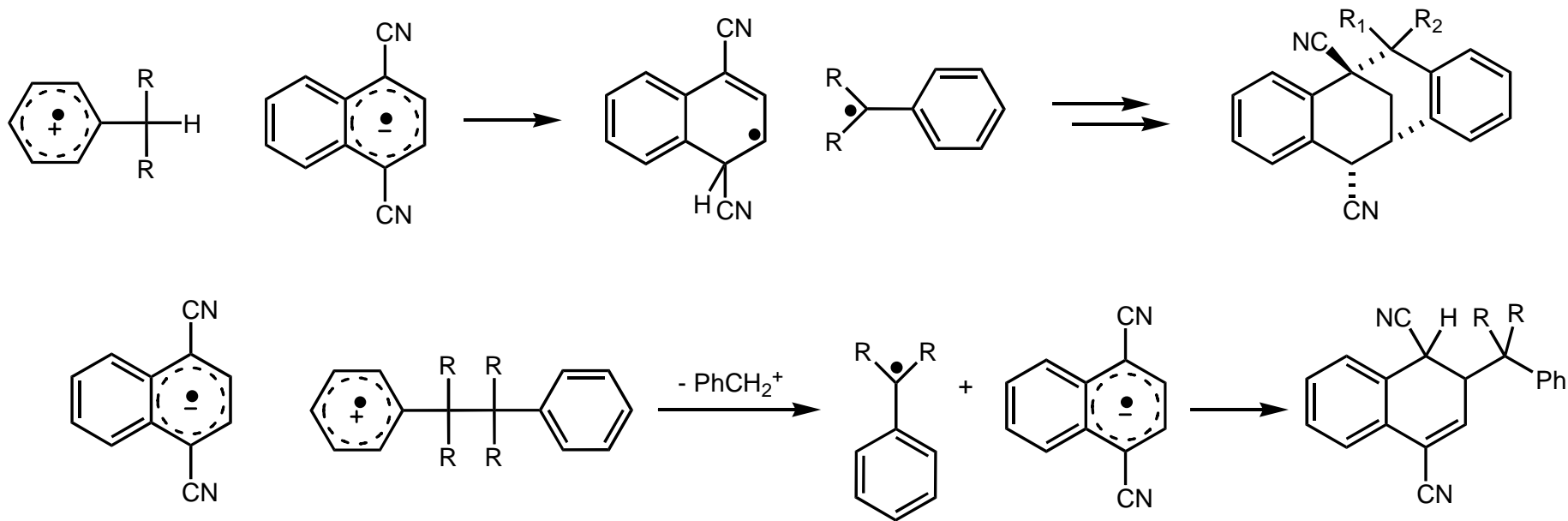
4

2
 $\text{R}_1 = \text{H}, \text{R}_2 = \text{Ph}$

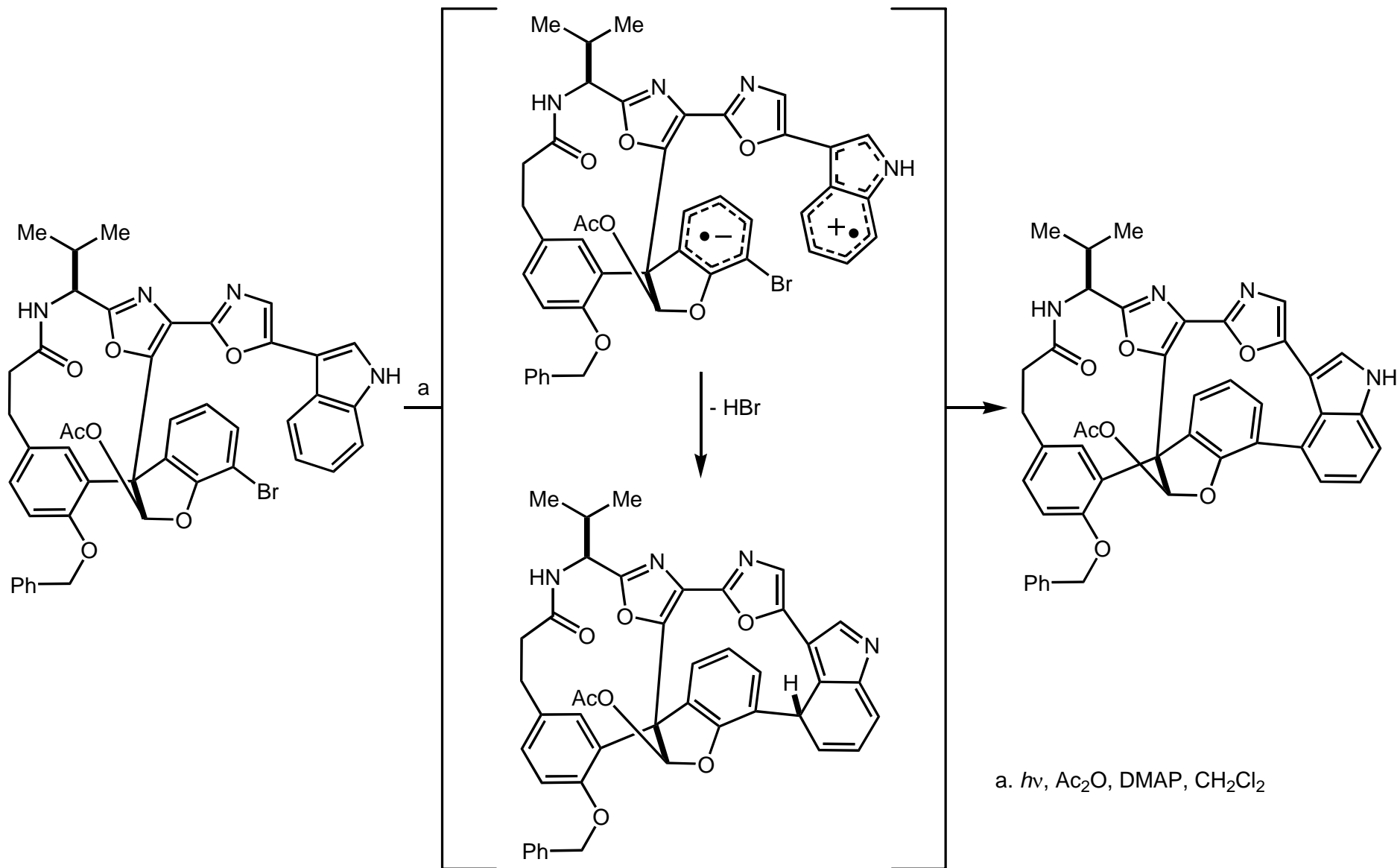


Mechenistic Pathways to Competing Products

C-H vs. C-C Bond Cleavage



Synthesis of a Precursor to Diazonamide A

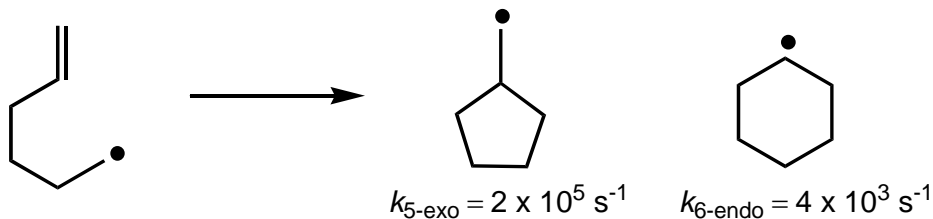


Outline

- The Basics
- Formation of Iminium Ions
- Reactions Involving Iminium Ions
- Carbonyl Reductions Using Amines
- Arene Acceptor Reactions
- **Cyclizations**

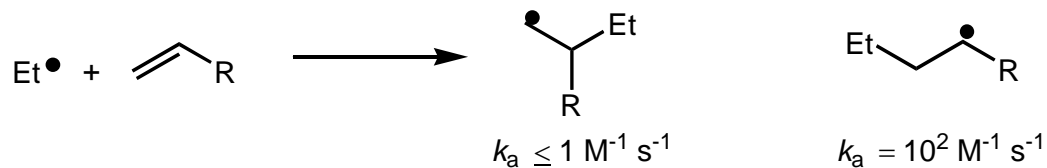
Radical Cyclizations

Hexenyl Radical Cyclizations



*Highly exothermic
Kinetically controlled*

vs.



Not formed

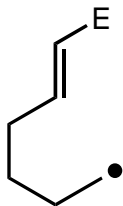
5-exo chair 0 kcal/mol

5-exo boat +1 kcal/mol

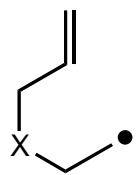
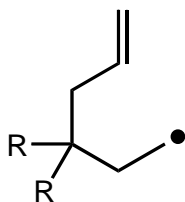
6-endo chair +3 kcal/mol

Accelerating and Decelerating Substituents

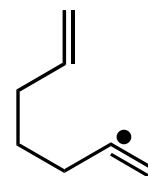
Substituents that accelerate 5-exo-trig cyclizations



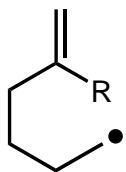
E= Electronegative Group



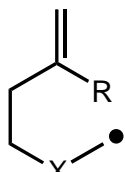
X= O, NR



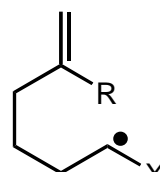
Substituents that decelerate 5-exo-trig cyclizations



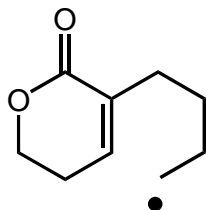
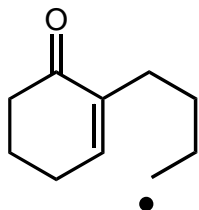
R ≠ H



X= O, NR

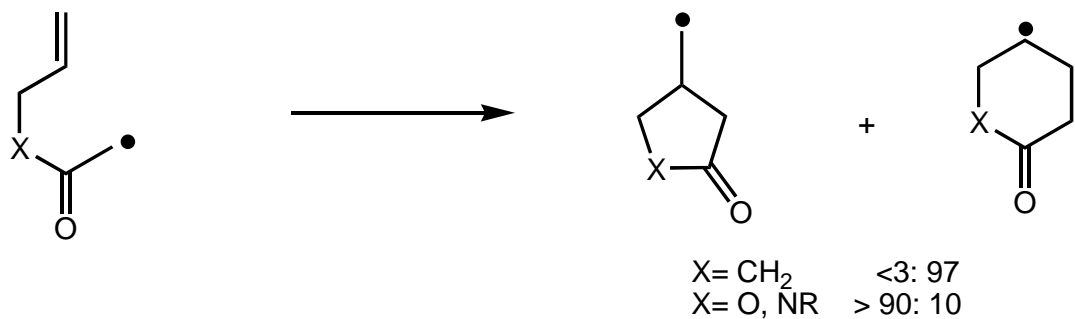
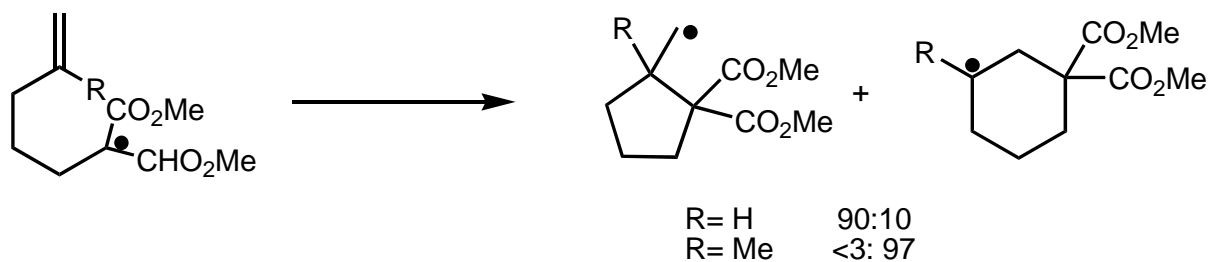


Substituents that accelerate 6-endo-trig cyclizations



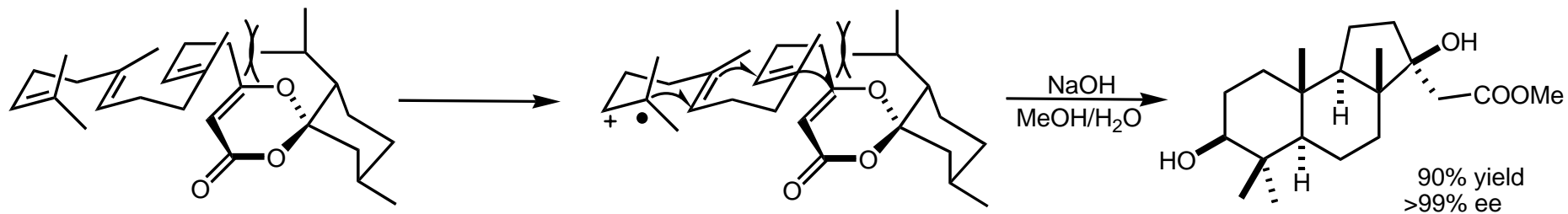
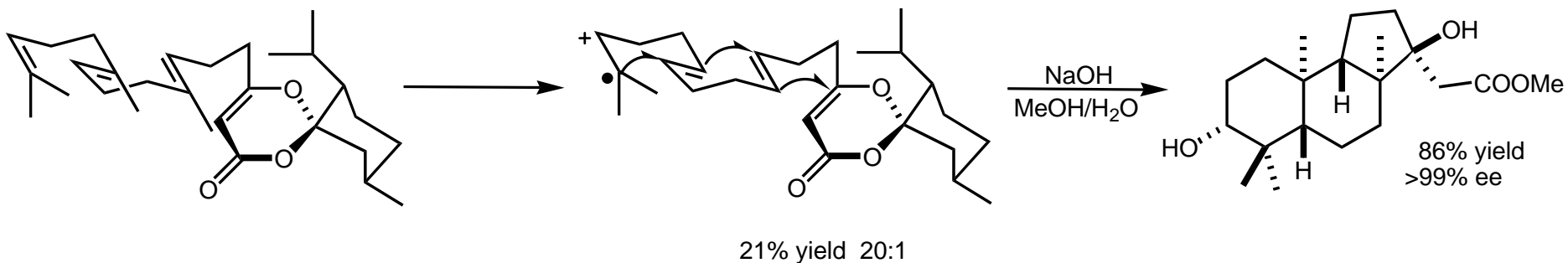
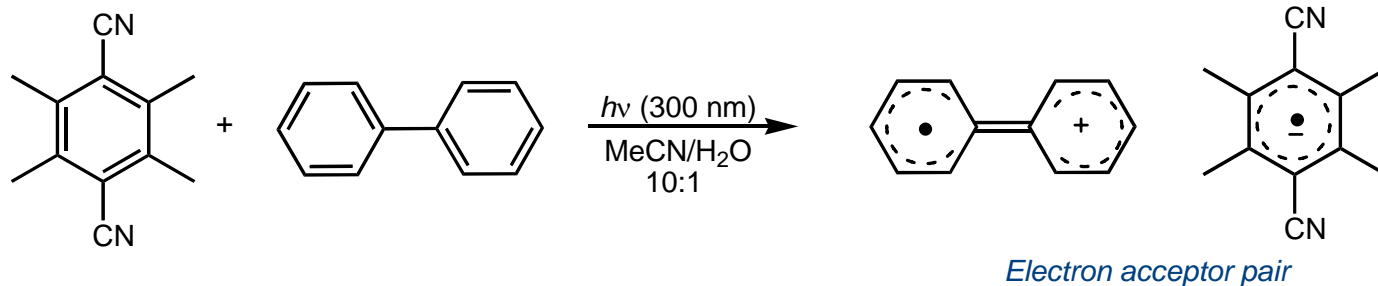
Carbonyl Substituted Radicals

6-endo-trig vs. 5-exo-trig

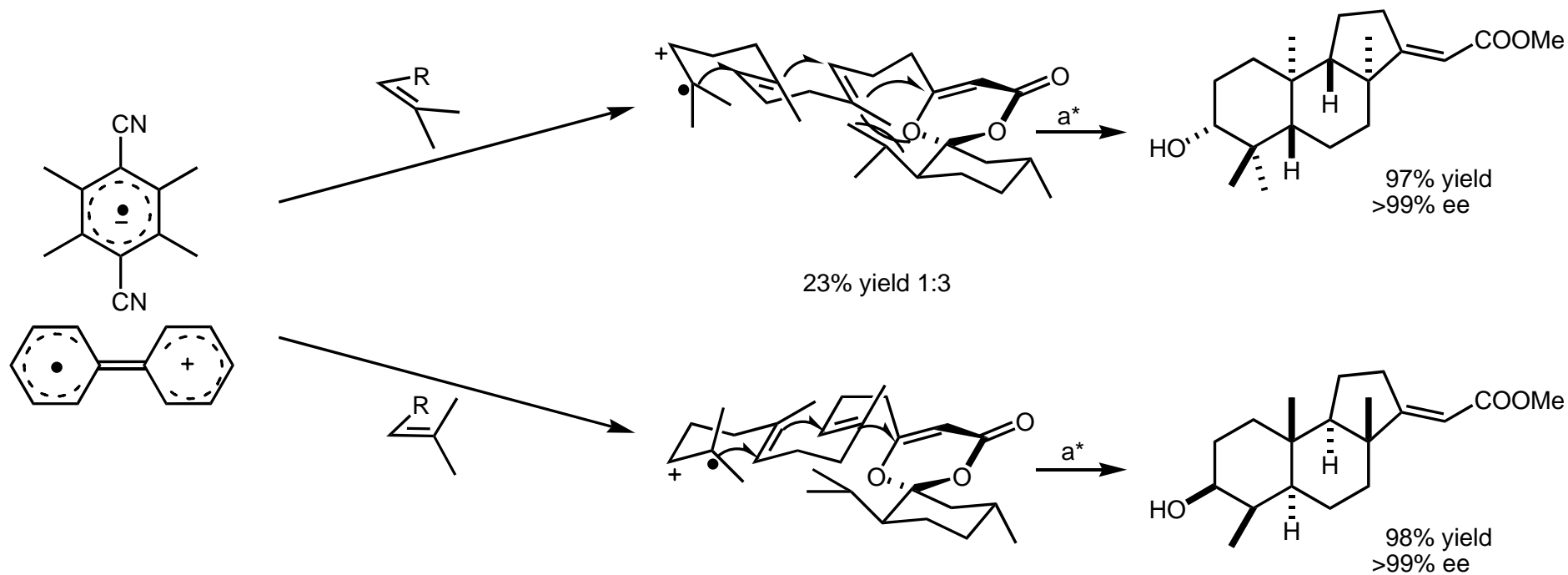


PET Cascade Cyclizations

Formation of Cyclic Terpenoids



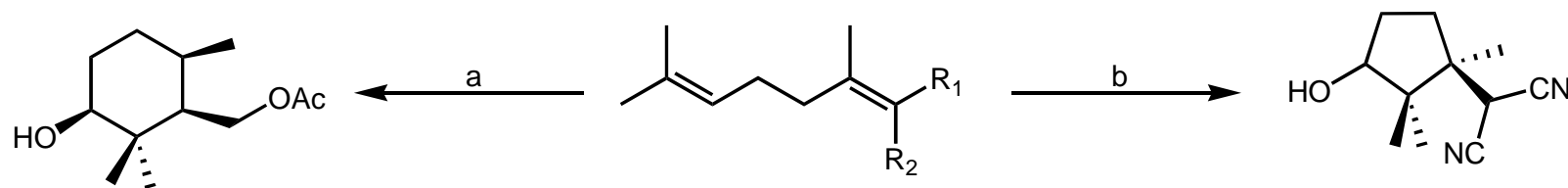
Cascade Cyclizations of Terpenoid Polyalkenes



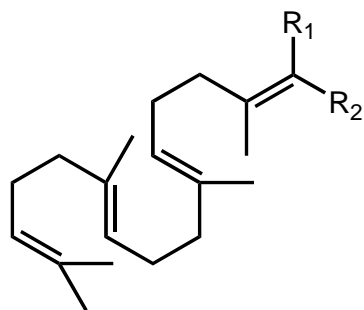
a* = 1. NaOMe, MeOH
2. SOCl₂, pyr.

Cyclization of Terpenoid Alkenes Via PET

6-endo-trig vs. 5-exo-trig



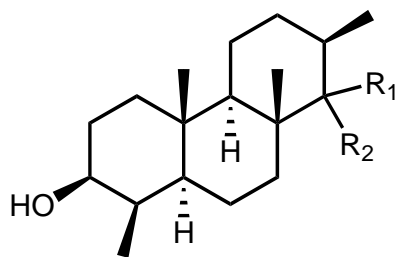
a: $R_1 = \text{CH}_2\text{OAc}$, $R_2 = \text{H}$
 b: $R_1 = \text{CN}$, $R_2 = \text{CN}$



$R_1 = \text{CH}_2\text{OAc}$, $R_2 = \text{H}$

$R_1 = \text{CN}$, $R_2 = \text{CN}$

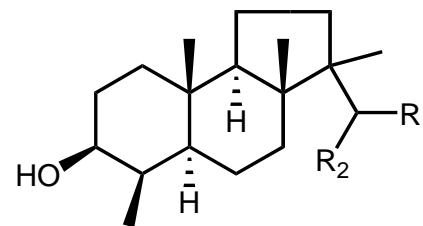
$R_1 = \text{H}$, $R_2 = \text{CO}_2\text{Et}$



100

0

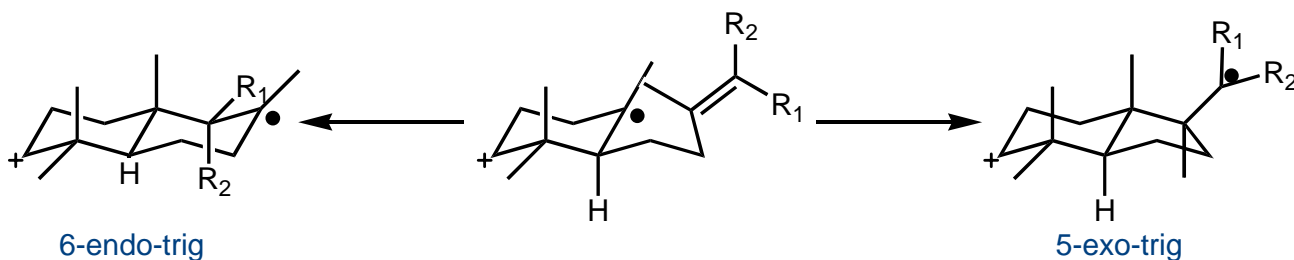
65



0

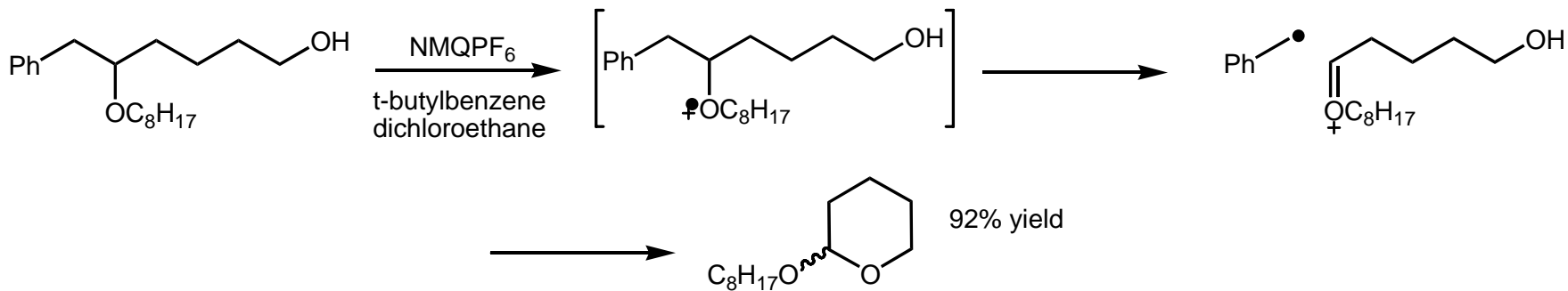
100

35



Cyclic Acetal Synthesis

Electron Transfer Initiated Cyclizations



Substrate	Product	Yield	D. R.
		74	-
		82	-
		55	-
		92	1.2:1
		84	1.7:1

Conclusions

- We should all go do our chemistry in the SUN!!!
- PET reactions generally involve mild reaction conditions that are tolerant to most functional groups
- A number of natural product cores containing nitrogen can be accessed via PET